Patent Right	Date	October 22, 2018	Court	Intellectual Property High Court, Second Division
	Case Number	2017 (Gyo-Ke)10106		
- A case in which, with regard to an invention titled "Treatment with anti-ErbB2 antibodies," since the configuration of different features could be easily conceived by a person skilled in the art based on the statements in cited documents and the effects of the Invention could be predicted by a person skilled art, the judgment of trial decision about inventive step is wrong.				

Case type : Rescission of Trial Decision to Maintain

Result : Granted

References : Article 29, paragraph 2 of Patent Act

Number of related rights, etc.: Patent No.5623681, Invalidation Trial No. 2016-800021

Summary of the Judgment

1. The case is a lawsuit for revocation of a trial decision which invalidates the demand for invalidation trial of patent concerning the invention titled "Treatment with anti-ErbB2 antibodies."

The trial decision judged that the reasons for invalidation due to lack of novelty and lack of inventive step are groundless since [i] Patent Invention 1 is different from Cited Invention in that a pharmaceutical formulation containing anti-HER2 antibody is applied to "a therapy comprising sequentially carrying out the steps of (a) treating a patient with the pharmaceutical formulation, (b) surgically removing cancer cells, and (c) treating the patient with the pharmaceutical formulation or a chemotherapeutic agent;" and [ii] the effects of Patent Invention 1 has been confirmed by publications after the priority date for the Invention and the effects stated in these publications could not be predicted from the statements of the cited documents.

2. Since Patent Invention 1 could be easily conceivable based on the statement in the cited document and the effects of the invention could be easily predictable by a person skilled in the art, the judgment rescinded the trial decision as follows:

(1) Regarding the easily-conceived property of the different features

A The pharmaceutical formulation of the invention stated in the package insert of Herceptin (Exhibit Ko1 Invention) is a pharmaceutical formulation containing a therapeutically effective amount of anti-HER2 antibody. At the time of the priority date for the Invention, the common general technical knowledge included the following matters: [i] the anti-HER2 antibody binds to the extracellular region of the HER2 protein to suppress proliferation of breast cancer cells overexpressing the HER2 protein and to cause antibody-dependent cell-mediated cytotoxicity (ADCC);

[ii] overexpression of HER2 protein is observed not only in metastatic breast cancer but also in 25% to 30% of early stage breast cancer; [iii] in clinical trials of patients with metastatic breast cancer with tumors overexpressing HER2 protein, compared with the single administration group of a specific chemotherapeutic agent including paclitaxel, enhancement of antitumor effects was observed such that the time-period of disease progression (time to disease progression) was prolonged in the group of combination administration of the chemotherapeutic agent and the anti-HER2 antibody, overall response (ORR) was improved, and the median of the reaction period was prolonged, the survival rate for one year was increased, and enhanced antitumor effects were observed; [iv] in a clinical trials of anti-HER2 antibody, even when administered alone or in combination with a chemotherapeutic agent, the cases where HER2 protein was more strongly expressed tended to show more excellent antitumor effects and time to disease progression; and [v] development of a therapeutic drug for breast cancer confirms the anticancer effect on patients with operable breast cancer based on the anti-cancer effects on patients with metastatic breast cancer.

By taking these matters together with the fact that Exhibit Ko 2 suggests preoperative prescription of combining anti-HER2 antibody and chemotherapy for a patient with early-stage breast cancer, a person skilled in the art touching Exhibit Ko 1 could easily conceive of applying the pharmaceutical formulation stated in the invention of Exhibit Ko 1, which is one containing a therapeutically effective amount of anti-HER2 antibody, to the treatment of operable breast cancer overexpressing HER2 protein.

B In addition to the above [iii], [vi] in breast cancer, the success or failure of breast conservation generally has a great influence on the female quality of life (QOL) and thus preoperative adjunctive therapy has been shown to make operation easier and allow breast conservation at a high rate; and [vii] operable breast cancer is commonly treated by subjecting to preoperative chemotherapy, surgically removing the tumor, and performing postoperative adjuvant chemotherapy in this order. Subsequently, for the treatment of operable breast cancer overexpressing HER2 protein, these matters of the technical common sense at the time of the priority date for the Invention are taken together with the matters suggested in Exhibit Ko 2 as stated in the above A to allow a person skilled in the art touching Exhibit Ko 1 to easily conceive of administrating the pharmaceutical formulation of Invention 1 together with a chemotherapeutic agent prior to surgery, performing the surgery, and then administrating the pharmaceutical formulation of Exhibit Ko 1 Invention together with a chemotherapeutic agent.

(2) Regarding the effects of Patent Invention 1

The corrected description does not indicate the results of clinical trials and so on and remains in the statement that "patients who have been treated according to the above treatment methods will generally show improved survivors and/or extended time of tumor progression (TTP)."

In breast cancer, survival rate and time of tumor progression (TTP) are general indicators for the effects of an anticancer drug. The effects of Patent Invention1 are just qualitative effects that the pharmaceutical formulation of Patent Invention 1 shows improved survival rate and extended time of tumor progression (TTP) as compared with the case where the pharmaceutical formulation of Patent Invention 1 is not administered.

According to the statement in Exhibit Ko 1, a person skilled in the art could recognize that the pharmaceutical formulation of the Exhibit Ko 1 Invention has qualitative effects of improving the survival rate and extending the time of tumor progression (TTP) for patients with metastatic breast cancer overexpressing HER2 protein. When the pharmaceutical formulation of the Exhibit Ko 1 Invention is applied to operable breast cancer overexpressing HER2 protein by the process of Patent Invention 1, compared with the case without this administration, it has qualitative effects of improving the survival rate and extending the time of tumor progression (TTP). This matter could be predictable by a person skilled in the art.

Experimental data of publications after the priority date cited by the trial decision could be taken into consideration within the scope of statement in the corrected description to the extent that the data shows the above qualitative effects. The qualitative effects could be predictable by a person skilled in the art. Therefore, it cannot be said that the data shows remarkable effects. On the other hand, referring to the experimental data beyond the qualitative effects is beyond the scope of the statement in the corrected description, and thus cannot be taken into account as the effects of Patent Invention 1.

Judgment rendered on October 22, 2018
2017 (Gyo-Ke) 10106 A case of seeking rescission of JPO decision
Date of conclusion of oral argument: July 11, 2018

Judgment

Indication of parties concerned As per attachment "List of parties concerned"

Main text

1. The decision on Invalidation Trial No. 2016-800021 that JPO made on December 27, 2016 shall be rescinded.

2. The court costs (including the cost for supporting intervention) shall be borne by Defendant.

3. An additional period for a final appeal against this judgment and a petition for acceptance of the final appeal shall be determined as 30 days.

Facts and reasons

No. 1 Claim

The same as the main text

No. 2 Background

This case is a suit against a trial decision that dismissed a request for trial for patent invalidation. The issue is the presence or absence of errors in the determination of novelty and inventive step.

1 History of the procedures in JPO

Defendant filed a patent application on May 9, 2000, for an invention titled "TREATMENT WITH ANTI-ErbB2 ANTIBODIES" (Japanese Patent Application No. 2000-617920 claiming priority benefit under the Paris Convention with a priority date of May 14, 1999 [hereinafter referred to as "the priority date"] in the United States), and the patent was registered on October 3, 2014 (Patent No. 5623681, Number of claims: 9, hereinafter this patent is referred to as "the Patent"; Exhibit Ko 22).

Plaintiff filed a request for trial for patent invalidation (Invalidation Trial No. 2016-800021) for the inventions according to Claims 1 to 9 of the Patent on February 15, 2016 (Exhibit Ko 23). Defendant filed a request for correction to correct the description on June 21, 2016 (hereinafter referred to as "the Correction". Exhibit Ko 25).

JPO made a decision on December 27, 2016 to the effect that "the correction to correct the description of Patent No. 5623681 as per the corrected description attached to a request for correction on June 21, 2016 shall be accepted. A request for trial with regard to the patents of the inventions according to Claims 1 to 9 should be dismissed." Its certified copies were served to Plaintiff on January 10, 2017.

2 Summary of the patent invention

The recitation of the claims of the inventions according to Claims 1 to 9 of the Patent (hereinafter referred to as e.g. "patent invention 1" in accordance with the number of claims, and patent inventions 1 to 9 are collectively referred to as "the patent invention") is set forth below (further, the description and drawings of the Patent after the correction [Exhibits Ko 22, 25] are referred to as "the corrected description").

(1) Patent invention 1

[Claim 1]

A pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-ErbB2 antibody for the treatment of a human patient who has been diagnosed with breast tumor where ErbB2 protein is expressed, the treatment comprising implementing the following steps in the following order of: (a) treating the patient with the pharmaceutical; (b) surgically removing the tumor; and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent.

(2) Patent invention 2

[Claim 2]

The pharmaceutical of Claim 1, wherein the step (a) further comprises treating the patient with a therapeutically effective amount of a chemotherapeutic agent.

(3) Patent invention 3

[Claim 3]

The pharmaceutical of Claim 1, wherein the step (c) comprises treating the patient with the pharmaceuticals of Claim 1.

(4) Patent invention 4

[Claim 4]

The pharmaceutical of Claim 3, wherein the step (c) further comprises treating the patient with a therapeutically effective amount of a chemotherapeutic agent.

(5) Patent invention 5

[Claim 5]

The pharmaceutical of Claim 1, wherein a tumor overexpresses ErbB2 protein.

(6) Patent invention 6

[Claim 6]

The pharmaceutical of Claim 2, wherein a chemotherapeutic agent is a taxoid.

(7) Patent invention 7

[Claim 7]

The pharmaceutical of Claim 6, wherein the taxoid is paclitaxel or docetaxel.

(8) Patent invention 8

[Claim 8]

The pharmaceutical of Claim 4, wherein a chemotherapeutic agent is a taxoid.

(9) Patent invention 9

[Claim 9]

An article of manufacture comprising a container, a pharmaceutical of Claim 1 contained in the container, and a package insert instructing users of the composition to treat a patient in principle by implementing the following steps in the following order of: (a) treating the patient with the pharmaceutical; (b) surgically removing a tumor; and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent.

3 Demandant's (Plaintiff's) Allegation in trial (reasons for invalidation)

(1) Reason 1 for Invalidation (Lack of novelty on the basis of Exhibit Ko 1)

Patent inventions 1 to 8 are the inventions described in Exhibit Ko 1 (hereinafter referred to as "Exhibit Ko 1 invention"), and thus correspond to Article 29, paragraph (1), item (iii) of the Patent Act, and thus are not patentable.

Exhibit Ko 1: Genentech, Inc., the package insert of HERCEPTIN (registered trademark) (Trastuzumab), September 25, 1998

(2) Reason 2 for Invalidation (Lack of novelty on the basis of Exhibit Ko 2)

Since patent inventions 1 to 8 are described in Exhibit Ko 2, the inventions correspond to the inventions specified in Article 29, paragraph (1), item (iii) of the Patent Act and are thus not patentable.

Exhibit Ko 2: Valero V., Seminars in Oncology, April 1998, Vol. 25, No. 2, additional volume No. 3, pages 36 to 41

(3) Reason 3 for Invalidation (Lack of Inventive Step over Exhibit Ko 1 as a main cited reference)

Patent inventions 1 to 9 were easily conceivable before filing by a person ordinarily skilled in the art on the basis of descriptions of Exhibits Ko 1 to Ko 6, and thus cannot be granted a patent under Article 29, paragraph (2) of the Patent Act.

Exhibit Ko 3: Perez E.A., The Oncologist, 1998, Vol. 3, No. 6, pages 373 to 389

Exhibit Ko 4: Gradishar W.J., Oncology [online], August 1, 1997, [Searched on August 10, 2015], Internet, URL:http://(hereinafter omitted)

Exhibit Ko 5: Pegram M. and nine others, Oncogene, April 1, 1999, Vol. 18, No. 13, pages 2241 to 2251

Exhibit Ko 6: Ross J.S. and one other, The Oncologist, 1998, Vol. 3, No. 4,

pages 237 to 252

(4) Reason 4 for Invalidation (Lack of Inventive Step over Exhibit Ko 2 as a main cited reference)

Patent inventions 1 to 9 were easily conceivable before filing by a person ordinarily skilled in the art on the basis of Exhibits Ko 1, 2, 5, and 6 or Exhibits Ko 1 to 3, 5, and 6, and thus cannot be granted a patent under Article 29, paragraph (2) of the Patent Act.

(5) Reason 5 for Invalidation (Lack of Inventive Step over Exhibit Ko 3 as a main cited reference)

Patent inventions 1 to 9 were easily conceivable before filing by a person ordinarily skilled in the art on the basis of Exhibits Ko 1, 3, 5, and 6, and thus cannot be granted a patent under the Article 29, paragraph (2) of the Patent Act.

4 Summary of reasons for trial decision

(1) Reason 1 for Invalidation (Lack of novelty on the basis of Exhibit Ko 1)

A Patent invention 1

(A) The summary of Reason 1 for invalidation according to the patent invention 1 is set forth as below.

a Exhibit Ko 1 discloses the following Exhibit Ko 1 invention:

"A pharmaceutical comprising a therapeutically effective amount of Herceptin antibody for the treatment of a human patient who has been diagnosed with breast tumor where HER2 protein is overexpressed, the treatment comprising the steps of: (a) treating the patient with the pharmaceutical, and the step (a) is a step of treating the patient with the pharmaceutical, or the pharmaceutical and a therapeutically effective amount of a chemotherapeutic agent such as paclitaxel, anthracycline, cyclophosphamide, doxorubicin, or epirubicin."

b Patent invention 1 and Exhibit Ko 1 invention have the following common point in common and differ from each other in the following Different feature 1:

(Common point)

"A pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-ErbB2 antibody for the treatment of a human patient who has been diagnosed with breast tumor where ErbB2 protein is expressed"

(Different feature 1)

Patent invention 1 applies the pharmaceutical to the treatment that implements the steps of (a) treating a patient with the pharmaceutical, (b) surgically removing a tumor; and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent, in this order, whereas Exhibit Ko 1 invention fails to specify the application of

the pharmaceutical to the treatment implementing such steps sequentially.

c It was a matter of common technical knowledge as of the filing to implement the treatment with preoperative administration of pharmaceutical, removal of tumor by surgery, and the treatment with postoperative administration of pharmaceutical as a common process of the treatment of breast cancer (Exhibits Ko 2, 4).

Further, according to Patent and Utility Model Handbook, Appendix B, Chapter 3, 2.2(3)(3-2-2), to find novelty, a specific dose regimen and dosage amount must be based on the properties of the compound.

Consequently, regardless of the kinds of pharmaceutical to be administered, Different feature 1 of matters according to a commonly practiced dose regimen is not based on the properties of humanized 4D5 anti-ErbB2 antibody, which is an active ingredient of a pharmaceutical according to Patent invention 1. Thus this difference in dose regimen is pushed aside in determining the presence or absence of novelty of Patent invention 1.

d Therefore, Different feature 1 is not a substantial difference.

(B) However, Patent invention 1 includes a pharmaceutical use of applying a pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-ErbB2 antibody to a tumor with a specific dose regimen comprising the above step (a) of treating a patient with the above pharmaceutical before surgically removing a tumor, and the subsequent steps (b) and (c) in a human patient who has been diagnosed with breast tumor where ErbB2 protein is expressed, as a matter for specifying the invention. Further, the above pharmaceutical use is based on nothing less than the properties of the above antibody.

On the other hand, Exhibit Ko 1 invention does not apply a pharmaceutical comprising humanized 4D5 anti-ErbB2 antibody with the above specific dose regimen to breast tumor where ErbB2 protein is expressed, nor can it be seen from the whole disclosure of Exhibit Ko 1 that a pharmaceutical comprising the antibody is used for the above specific dose regimen.

Therefore, Different feature 1 is a substantial difference. It cannot be said that Patent invention 1 is Exhibit Ko 1 invention.

B Patent inventions 2 to 8

Patent inventions 2 to 8 depending from Patent invention 1 are inventions that are further restricted. Thus, for a similar reason to the aforesaid item A directed to Patent invention 1, the patent for these inventions could not be invalidated by the reason 1 for invalidation.

(2) Reason 2 for Invalidation (Lack of novelty on the basis of Exhibit Ko 2)

A Patent invention 1

(A) The summary of Reason 2 for invalidation according to Patent invention 1 is as in the following.

a Exhibit Ko 2 describes the following invention (hereinafter referred to as " Exhibit Ko 2 invention-1-1").

"A pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-ErbB2 antibody for the treatment of a human patient who has been diagnosed with breast tumor where ErbB2 protein is expressed, the treatment comprising (a) the step of treating a patient with the pharmaceutical"

b According to the description of "the test in progress combines recombinant human HER2 monoclonal antibody with other agents such as doxorubicin, cisplatin, or paclitaxel. Further, a randomized Phase III test targets doxorubicin and cyclophosphamide in combination with or not in combination with recombinant human HER2 monoclonal antibody as a first-line treatment for metastatic disease" of Exhibit Ko 2, Exhibit Ko 2 describes the following invention (hereinafter referred to as "Exhibit Ko 2 invention-1-2"):

"A pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-ErbB2 antibody for the treatment of a human patient who has been diagnosed with breast tumor where ErbB2 protein is expressed, the treatment comprising (a) the step of treating a patient with the pharmaceutical, and the step (a) is a step of treating a patient with the pharmaceutical or the pharmaceutical and a therapeutically effective amount of a chemotherapeutic agent such as doxorubicin, cisplatin, paclitaxel, or cyclophosphamide"

c Summarizing the aforesaid items a and b, Exhibit Ko 2 describes the following invention (hereinafter referred to as " Exhibit Ko 2 invention-1"):

"A pharmaceutical comprising a therapeutically effective amount of Herceptin antibody for the treatment of a human patient who has been diagnosed with breast tumor where HER2 is overexpressed, the treatment comprising (a) the step of treating the patient with the pharmaceutical, and the step (a) is a step of treating the patient with the pharmaceutical, or the pharmaceutical and a therapeutically effective amount of a chemotherapeutic agent such as doxorubicin, cisplatin, paclitaxel, or cyclophosphamide."

d In addition, according to the description of "The role of these novel strategies in conjunction with primary chemotherapy should be assessed in patients with early breast cancer", "Biologically - genetically new treatment" and the remaining description of Exhibit Ko 2, Exhibit Ko 2 describes the following invention

(hereinafter referred to as " Exhibit Ko 2 invention-2").

"A pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-ErbB2 antibody for the treatment of a human patient who has been diagnosed with breast tumor where ErbB2 protein is expressed, wherein the pharmaceutical is applied to the treatment of a breast cancer patient to be implemented in the order of preoperative therapy, surgery, and postoperative therapy in combination with chemotherapy, wherein a chemotherapeutic agent used for said chemotherapy includes any of doxorubicin, cisplatin, paclitaxel, and cyclophosphamide"

e Patent invention 1 and Exhibit Ko 2 invention-2 have in common that "a pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-ErbB2 antibody for the treatment of a human patient who has been diagnosed with breast tumor where ErbB2 protein is expressed". Further, the treatment of Patent invention 1 comprising implementing the steps in the order of: (a) treating a patient with a pharmaceutical; (b) surgically removing a tumor; and (c) treating the patient with the pharmaceutical or a chemical therapeutic agent has substantially no difference from the treatment that applies a pharmaceutical in combination with chemotherapy in the order of preoperative therapy, surgery, and postoperative therapy for the treatment of breast cancer patients.

(B) Exhibit Ko 2 describes Exhibit Ko 2 invention-1-1; however, the description of "the test in progress combines recombinant human HER2 monoclonal antibody with other agents such as doxorubicin, cisplatin, and paclitaxel. Further, randomized Phase III test targets doxorubicin and cyclophosphamide in combination with or not in combination with recombinant human HER2 monoclonal antibody as a first-line treatment for metastatic disease" of the aforesaid item (A)b only introduces the presence of test in progress, and does not disclose a pharmaceutical invention that a person ordinarily skilled in the art could implement. Thus it cannot be said that Exhibit Ko 2 invention-1-2 (and Exhibit Ko 2 invention-1 that premises this) is described.

Further, a part of the description of Exhibit Ko 2 on which Demandant (Plaintiff) relies in the aforesaid item (A)d describes a neoadjuvant therapy using only a chemotherapeutic agent. It is different from the descriptions of Exhibit Ko 2 invention-1-1 and Exhibit Ko 2 invention-1-2. Thus it cannot be said that a combination of this with Exhibit Ko 2 invention-1-1 and Exhibit Ko 2 invention-1-2 describes Exhibit Ko 2 invention-2.

Therefore, it cannot be said that Patent invention 1 is Exhibit Ko 2 invention-2.

B Patent inventions 2 to 8

Patent inventions 2 to 8 are inventions further restricted by citing Patent invention 1. Thus for a similar reason to the aforesaid item A according to Patent invention 1, the patent for these inventions could not be invalidated by Reason 2 for invalidation.

(3) Reason 3 for Invalidation (Lack of Inventive Step over Exhibit Ko 1 as a main cited reference)

A Patent invention 1

(A) The summary of Reason 3 for invalidation according to Patent invention 1 is set forth as below.

a Whether a constitution was easily conceivable

Even if Different feature 1 should be a substantial difference, it was a matter of common technical knowledge as of the filing to implement the treatment with preoperative administration of pharmaceutical, removal of tumor by surgery, and postoperative administration of pharmaceutical as a common process of the treatment of breast cancer (Exhibits Ko 2, 4).

Further, Exhibit Ko 2 describes the use of humanized 4D5 anti-ErbB2 antibody for the treatment involving surgery of patients with breast cancer.

Furthermore, Exhibit Ko 3 also describes the use of humanized 4D5 anti-ErbB2 antibody for the treatment involving surgery of patients with breast cancer where HER2 receptor is overexpressed.

Consequently, a person ordinarily skilled in the art could have easily conceived of using a pharmaceutical of Exhibit Ko 1 invention, which was used as a pharmaceutical invention for the treatment of a breast cancer, for the treatment involving surgery, and then further using the pharmaceutical in accordance with a common process of a breast cancer treatment involving surgery.

Specifically, a person ordinarily skilled in the art could have easily conceived of applying the pharmaceutical of Exhibit Ko 1 invention to the treatment that implements the steps of (a) treating a patient with the pharmaceutical, (b) surgically removing a tumor, and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent, in this order.

b The effects caused

(a) The corrected description discloses in [0119] that "patients treated according to the above therapeutic regimen will display improved overall survival and/or reduced time to tumor progression (TTP)." This description is a future tense simply expressing hope or expectation. Thus it does not support the effect of Patent

invention 1.

Further, it can be seen from the description of Exhibit Ko 1 that Exhibit Ko 1 invention causes the effect of "experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a higher one-year survival rate". Thus it cannot be said that the effects of the corrected description of [0119] are more advantageous effects that a person ordinarily skilled in the art could not expect compared to Exhibit Ko 1 invention.

(b) The corrected description describes the purpose of "reduce the size of, or eliminate, the tumor" in [0118]. This is not a description showing that the effects are caused. Furthermore, according to the description of Exhibit Ko 5, it is demonstrated that a tumor size is reduced in a living body by Herceptin treatment in combination with a chemotherapeutic agent. Even if the above purpose is achieved, this effect shows a unique property possessed by a combined pharmaceutical of chemotherapeutic agent and herceptin. It cannot be said to be an advantageous effect that a person ordinarily skilled in the art could not expect in comparison to the cited invention.

(c) The corrected description describes the purpose of "reduce the likelihood of disease recurrence" in [0119] as a problem. This is not a description showing that the effects are caused. Furthermore, Exhibit Ko 6 discloses the extension of time until recurrence by a therapy with a single dose of herceptin or a combined therapy of herceptin and a chemotherapeutic agent. Even if the above problem is achieved, this effect shows a unique property possessed by herceptin. It cannot be said to be an advantageous effect that a person ordinarily skilled in the art could not expect in comparison to the cited invention.

(d) Demandee alleges significant effects that go beyond the expectation of a person ordinarily skilled in the art in the written opinion on the basis of Exhibit Ko 17 [Trial Exhibit Otsu 1] published after the filing (Buzdar A.U. and 19 others, Journal of Clinical Oncology, June 1, 2005, Vol. 23, No. 16, pages 3676 to 3685), and alleges that "The addition of trastuzumab to preoperative chemotherapy could significantly increase pathological Complete Response (pCR) without involving clinical development of congestive heart failure".

Regarding the effects as alleged in the written opinion after filing, however, when the description describes an advantageous effect compared to the cited invention and when a person ordinarily skilled in the art could infer the advantageous effect compared to the cited invention from the description or drawings, while it is silent

about the advantageous effect compared to the cited invention, the effect alleged and proved in the written opinion (e.g. experimental result) should be considered, whereas if the effect as alleged and proved in the written opinion which is not described in the description and a person ordinarily skilled in the art could not infer from the description or drawings should not be considered. The effects of suppressing the development of congestive heart failure are not described in the description. Thus the effect of "could significantly increase pathological Complete Response (pCR) without involving clinical development of congestive heart failure" as alleged in the written opinion after filing should not be considered in the determination of inventive step.

Even if the above effect should be considered, this effect shows a unique property possessed by herceptin. Thus it cannot be said to be an advantageous effect that a person ordinarily skilled in the art could not expect in comparison to the cited invention.

Further, the abstract of Exhibit Ko 17 [Trial Exhibit Otsu 1] points out that safety has not been established with fewer number of cases compared to Exhibit Ko 1. It cannot be said that Exhibit Ko 17 [Trial Exhibit Otsu 1] supports the fact that the effect alleged in the written opinion by Demandee is an advantageous effect that could not be expected compared to the cited invention.

(B) However, Patent invention 1 is different from Exhibit Ko 1 invention in the different feature 1; i.e., applying the pharmaceutical comprising humanized 4D5 anti-ErbB2 antibody to the treatment that implements the steps of (a) treating a patient with the pharmaceutical, (b) surgically removing a tumor; and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent, in this order.

Further, Patent invention 1 adopts this point, thereby allegedly causing the effect that "will display improved overall survivors and/or the reduced Time to Tumor Progression (TTP)" of the corrected description ([0119]). These effects are actually observed in Exhibits Ko 17 to 21 [Trial Exhibits Otsu 1 to 5]. Thus the effect of trastuzumab shown in Exhibits Ko 17 to 21 [Trial Exhibits Otsu 1 to 5] should be considered as the effect of Patent invention 1.

Exhibit Ko 17 [Trial Exhibit Otsu 1] shows that the improvement of pCR in patients with operable breast cancer was 41.7% (66.7% [Trastuzumab + chemotherapy group, n=16] - 25% [Chemotherapy group, n=18]) and 40.4% (66.7% [Trastuzumab + chemotherapy group, n=23] - 26.3% [Chemotherapy group, n=19]). Exhibit Ko 19 [Trial Exhibit Otsu 3] (Gianni L. and 19 others, Lancet, January 30, 2010, Vol. 375, No. 9712, pages 377 to 384) shows that the improvement on pCR in patients with

locally advanced or inflammatory breast cancer was 21% (43% [combined with Trastuzumab] - 22% [not combined]) for breast tissue, and 19% (38% [combined with Trastuzumab] - 19% [not combined]) for breast tissues and entire axillary nodes, and shows the improvement on survival rate with no event for 3 years (Note that Exhibit Ko 18 [Trial Exhibit Otsu 2], which relates to Exhibit Ko 19 [Trial Exhibit Otsu 3] from authors and description, also describes a result similar to that of Exhibit Ko 19 [Trial Exhibit Otsu 3] in the study of "NOAH test".).

In contrast, the overall response rate, response durations, and one-year survival rate of Exhibit Ko 1 in clinical test for metastatic breast cancer patients, "targeted response rate" in a test for breast cancer patients of stage IV according to Exhibit Ko 2 invention-1-1 of Exhibit Ko 2 (it is assumed to mean the overall response rate in view of the description corresponding to Exhibit Ko 2-2 [Table 4, etc.] cited by Exhibit Ko 2; further, out of the overall response rate of 11.6%, the complete response rate is 2.3% [1 case] in the above description of Exhibit Ko 2-2.), the overall response rate and a median value of time-to-tumor progression in clinical tests for metastatic breast cancer of Exhibit Ko 3, and the increase of time for recurrence and the overall response rate in phase III clinical test for metastatic breast cancer of Exhibit Ko 6 are all treatment results for metastatic breast cancer. It is different in stage of disease from operable breast cancer for which a therapeutic effect is shown in Exhibit Ko 17 [Trial Exhibit Otsu 1] and Exhibit Ko 19 [Trial Exhibit Otsu 3].

Further, this operable breast cancer is an earlier disease stage compared to metastatic breast cancer for which a therapeutic effect is shown in the above Exhibits Ko 1 to 3 and Exhibit Ko 6; however, it cannot be said that a person ordinarily skilled in the art could expect from the therapeutic effect such as the complete response rate of 2.3% in the above Exhibit Kos that the improvement of the above pCR to the extent of 41.7% or 40.4% and the improvement of survival rate with no events for 3 years would be achieved.

Further, the reduction of xenograft volume in a test for athymic mouse grafted with HER2/neu genetically transformed MCF7 humanized breast cancer cell of Exhibit Ko 5 is a result in an animal experiment. Therefore, it cannot be said all the more that a person ordinarily skilled in the art could expect that a therapeutic effect shown in Exhibit Ko 17 [Trial Exhibit Otsu 1] and Exhibit Ko 19 [Trial Exhibit Otsu 3] might be achieved.

B Patent inventions 2 to 9

Patent inventions 2 to 9 are inventions further restricted by citing Patent invention 1. Thus for a similar reason to the aforesaid item A according to Patent

invention 1, the patent for these inventions could not be invalidated by the reason 3 for invalidation.

(4) Reason 4 for Invalidation (Lack of Inventive Step over Exhibit Ko 2 as a main cited reference)

A Patent invention 1

(A) The summary of Reason 4 for invalidation according to Patent invention 1 is set forth as below.

a Patent Invention 1 and Exhibit Ko 2 invention-1 have the following common point in common and differ from each other in the following Different feature 2:

(Common point)

"A pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-ErbB2 antibody for the treatment of a human patient who has been diagnosed with breast tumor where ErbB2 protein is expressed"

(Different feature 2)

Patent invention 1 applies the pharmaceutical to the treatment that implements the steps of (a) treating a patient with the pharmaceutical, (b) surgically removing a tumor, and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent, in this order, whereas Exhibit Ko 2 invention-1 fails to specify the application of the pharmaceutical to the treatment implementing such steps sequentially

b Exhibit Ko 2 discloses that "primary chemotherapy" means "preoperative chemotherapy". In view of the common technical knowledge that breast cancer patients are treated with preoperative chemotherapy, surgery, and postoperative chemotherapy, in this order, the description of "The role of these novel strategies in conjunction with primary chemotherapy should be assessed in patients with early breast cancer" of Exhibit Ko 2 means that the treatment with humanized 4D5 anti-ErbB2 antibody in combination with chemotherapy should be evaluated in breast cancer patients for which preoperative therapy, the removal of tumor by surgery, and postoperative therapy are implemented in this order. It motivates a person ordinarily skilled in the art to apply a pharmaceutical of Exhibit Ko 2 invention-1 to patients with early breast cancer and try to use it for the treatment before surgery with a pharmaceutical.

Therefore, a person ordinarily skilled in the art could have easily conceived of applying the treatment with the pharmaceutical for a method to treat breast cancer patients with preoperative therapy, surgery, and postoperative therapy of Exhibit Ko 2 in this order and implementing therapy with humanized 4D5 anti-ErbB2 antibody and chemotherapeutic agents on the basis of the above description in Exhibit Ko 2

invention-1.

Further, it was a matter of common general knowledge as of the filing of the Patent to implement adjuvant therapy solely by chemotherapy, as described in Exhibit Ko 2. A person ordinarily skilled in the art could easily conceive of doing so.

c The pharmaceutical of Exhibit Ko 2 invention-1 has achieved success in application to metastatic breast cancer patients. Exhibit Ko 3 shows the recognition that success may be expected even in the adjuvant and neoadjuvant settings as long as it is known that it will achieve success in a metastatic setting. Therefore, a person ordinarily skilled in the art could have easily conceived of applying the pharmaceutical to the treatment that implements the steps of (a) treating a patient with the pharmaceutical, (b) surgically removing a tumor; and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent, in this order, on the basis of the descriptions of Exhibit Ko 2 and Exhibit Ko 3 in Exhibit Ko 2 invention-1.

d For a similar reason to Reason 3 for invalidation, it cannot be said that the function and effect of the Patent invention 1 is an advantageous effect compared to the cited invention, nor is there observed an advantageous effect that goes beyond the expectation of a person ordinarily skilled in the art.

(B) As in the aforesaid item (2), however, it cannot be said that Exhibit Ko 2 describes Exhibit Ko 2 invention-1-2 (Exhibit Ko 2 invention-1). Thus Reason 4 for invalidation of Patent invention 1 lacking inventive step is not acceptable on the basis of this invention.

Further, even if a consideration should be given on the basis of Exhibit Ko 2 invention-1-1 in view of the circumstances of the case, it cannot be said that Patent invention 1 does not involve inventive step.

Specifically, comparing Patent invention 1 and Exhibit Ko 2 invention-1-1, Patent invention 1 is different from Exhibit Ko 2 invention-1-1 in applying the pharmaceutical comprising humanized 4D5 anti-ErbB2 antibody to the treatment that implements the steps of (a) treating a patient with the pharmaceutical, (b) surgically removing a tumor, and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent, in this order.

Further, Patent invention 1 adopts this point and causes the effects that "will display improved overall survivors and/or the reduced Time to Tumor Progression (TTP)" ([0119]) of the corrected description. These effects are actually confirmed in Exhibits Ko 17 to 21 [Trial Exhibits Otsu 1 to 5]. Further, similarly to the aforesaid item (3), it cannot be said that the above effects could be expected from the description of respective items of Exhibit Ko.

B Patent inventions 2 to 9

Patent inventions 2 to 9 are inventions further restricted by citing Patent invention 1. Thus for a similar reason to the aforesaid item A according to Patent invention 1, the patent for these inventions could not be invalidated by Reason 4 for invalidation.

(5) Reason 5 for Invalidation (Lack of Inventive Step over Exhibit Ko 3 as a main cited reference)

A Patent invention 1

(A) The summary of Reason 5 for invalidation according to Patent invention 1 is set forth as below.

a Exhibit Ko 3 describes the following invention (hereinafter referred to as the " Exhibit Ko 3 invention").

"A pharmaceutical comprising a therapeutically effective amount of Herceptin antibody for the treatment of a human patient who has been diagnosed with breast tumor where HER2 is overexpressed, the treatment comprising (a) the step of treating the patient with the pharmaceutical, and the step (a) is a step of treating the patient with the pharmaceutical and a therapeutically effective amount of paclitaxel."

b Patent Invention 1 and Exhibit Ko 3 invention have the following common point in common and differ from each other in the following Different feature 3:

(Common point)

"A pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-ErbB2 antibody for the treatment of a human patient who has been diagnosed with breast tumor where ErbB2 protein is expressed"

(Different feature 3)

Patent invention 1 applies the pharmaceutical to the treatment that implements the steps of (a) treating a patient with the pharmaceutical, (b) surgically removing a tumor, and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent, in this order, whereas Exhibit Ko 3 invention fails to specify the application of the pharmaceutical to the treatment implementing such steps sequentially

c Exhibit Ko 3 discloses that the combined therapy of herceptin antibody with chemotherapy brought a good result in a metastatic setting.

Further, Exhibit Ko 3 shows the recognition that success may be expected even in the adjuvant and neoadjuvant settings as long as it is known that it will achieve success in a metastatic setting.

Therefore, in Exhibit Ko 3 invention directed to a treatment with a pharmaceutical comprising a therapeutically effective amount of Herceptin antibody

for the treatment of a human patient who has been diagnosed with breast tumor where HER2 is overexpressed, a person ordinarily skilled in the art could have easily conceived of administering Herceptin and a chemotherapeutic agent prior to and after surgery on the basis of the description of Exhibit Ko 3.

d For a similar reason to Reason 3 for invalidation, it cannot be said that the function and effect of Patent invention 1 is an advantageous effect compared to the cited invention, nor is there observed the advantageous effect that goes beyond the expectation of a person ordinarily skilled in the art.

(B) However, Patent invention 1 is different from Exhibit Ko 3 invention in Different feature 3; i.e., applying the pharmaceutical comprising humanized 4D5 anti-ErbB2 antibody to the treatment that implements the steps of (a) treating a patient with the pharmaceutical, (b) surgically removing a tumor; and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent, in this order.

Further, Patent invention 1 adopts this point, thereby allegedly causing the effect that "will display improved overall survivors and/or the reduced Time to Tumor Progression (TTP)" of the corrected description ([0119]). These effects are actually confirmed in Exhibits Ko 17 to 21 [Trial Exhibits Otsu 1 to 5]. Further, similarly to the aforesaid item (3), it cannot be said that the above effects could be expected from the description of respective items of Exhibit Ko.

B Patent inventions 2 to 9

Patent inventions 2 to 9 are inventions further restricted by citing Patent invention 1. Thus for a similar reason to the aforesaid item A according to Patent invention 1, the patent for these inventions could not be invalidated by Reason 5 for invalidation.

(omitted)

No. 5 Judgment of this court

1 Regarding the patent invention

(1) The corrected specification (Exhibits Ko 22, 25) has the following descriptions:

A Field of the Invention

[0001]

... The present invention concerns the treatment of cancer with anti-ErbB2 antibodies.

B Background Art

[0002]

... Proto-oncogenes that encode growth factors and growth factor receptors have been identified to play important roles in the pathogenesis of various human malignancies, including breast cancer. It has been found that the human erbB2 gene (also known as HER2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer (Slamon et al., Science 235: 177-182 [1987]; Slamon et al, Science 244: 707-712 [1989]).

[0003]

Several lines of evidence support a direct role for ErbB2 in the pathogenesis and clinical aggressiveness of ErbB2-overexpressing tumors. The introduction of ErbB2 into non-neoplastic cells has been shown to cause their malignant transformation (Hudziak et al, Proc. Natl. Acad Sci. USA 84: 7159-7163 [1987]; DiFiore et al, Science 237: 78-182 [1987]). Transgenic mice that express HER2 were found to develop mammary tumors (Guy et al., Proc. Natl. Acad Sci. USA 89: 10578-10582 [1992]).

[0011]

A recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as rhuMAb HER2 or HERCEPTIN (registered trademark)) has been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anticancer therapy. (Baselga et al., J. Clin. Oncol 14: 737-744 [1996]).

[0012]

... rhuMab HER2 was shown to enhance the activity of paclitaxel (TAXOL (registered trademark)) and doxorubicin against breast cancer xenografts in nude mice injected with BT-474 human breast adenocarcinoma cells, which express high levels of HER2 (Baselga et al., Breast Cancer, Proceedings of ASCO, Vol. 13, Abstract 53 [1994]).

C Summary of the Invention

[0013]

In a first aspect, the present invention provides a method of treating a human patient susceptible to a tumor in which ErbB2 protein is expressed or diagnosed with a tumor in which ErbB2 protein is expressed, the method comprising the following steps, performed sequentially:

(a) treating the patient with a therapeutically effective amount of an anti-ErbB2 antibody and, optionally, further comprising treating the patient with a therapeutically effective amount of a chemotherapeutic agent (e.g. a taxoid, such as paclitaxel or doxetaxel);

(b) surgically removing the tumor; and then
(c) treating the patient with a therapeutically effective amount of an anti-ErbB2 antibody and/or of a chemotherapeutic agent (e.g. a taxoid, such as paclitaxel or doxetaxel).
[0014]

Preferably, the tumor overexpresses ErbB2 protein and is selected from the group consisting of a breast tumor, squamous cell tumor, small-cell lung tumor, non-small cell lung tumor, gastrointestinal tumor, pancreatic tumor, glioblastoma, cervical tumor, ovarian tumor, liver tumor, bladder tumor, hepatoma, colon tumor, colorectal tumor, endometrial tumor, salivary gland tumor, kidney tumor, prostate tumor, vulval tumor, thyroid tumor, hepatic carcinoma and a various kind of head tumor, and neck tumor.

The invention further provides an article of manufacture comprising a container, a composition within the container comprising an anti-ErbB2 antibody, and a package insert indicating that the composition is usable to treat a patient essentially according to the above method.

D Detailed Description of the Preferred Embodiments

(A) Definition
[0015]

... The terms "HER2", "ErbB2", and "c-Erb-B2" are used interchangeably. Unless indicated otherwise, the terms "ErbB2", "c-Erb-B2", and "HER2" refer to human protein, and "Her2", "erbB2" and "c-erb-B2" refer to human genes. The human erbB2 gene and ErbB2 protein are, for example, described in Semba et al., PNAS (USA) 82: 6497-6501 (1985) and Yamamoto et al. Nature 319: 230-234 (1986) (Genebank accession number X03363). ErbB2 comprises four domains (Domains 1-4).
[0043]

The term "therapeutically effective amount" refers to an amount of a drug effective to treat a disease or disorder in a mammal. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the disorder. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can, for example, be measured by assessing

the time to tumor progression (TTP), determining the response rate (RR), and/or evaluating overall survival.

[0047]

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially an ErbB2-overexpressing cancer cell either in vitro or in vivo. Thus, the growth inhibitory agent is one which significantly reduces the percentage of ErbB2 overexpressing cells in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest; for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogene, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995), especially p. 13. The 4D5 antibody (and functional equivalents thereof) can also be employed for this purpose.

[0052]

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications, and/or warnings concerning the use of such therapeutic products.

(B) Treatment with the Anti-ErbB2 Antibodies

[0105]

... The invention herein provides a three-step method for treating a human patient susceptible to or diagnosed with a tumor (or tumors) in which ErbB2 protein is expressed. Generally, the tumor to be treated is a primary tumor. In the first step, a therapeutically effective amount of an anti-ErbB2 antibody is administered to the patient in order to reduce the size of, or eliminate, the tumor (or tumors) in the patient prior to surgery. The patient is optionally further treated with one or more chemotherapeutic agents prior to surgery. In the second step, the tumor is surgically removed according to standard surgical procedures (e.g. lumpectomy or mastectomy). Following surgery, in the third step, a therapeutically effective amount of an anti-ErbB2 antibody, or of at least one chemotherapeutic agent, is administered to the patient in order to reduce the likelihood of disease recurrence. Generally, an anti-

ErbB2 antibody will be administered to the patient following surgery and, optionally, one or more chemotherapeutic agents will further be administered to the patient during this phase of the therapy.

[0108]

Where the anti-ErbB2 antibody is combined with a chemotherapeutic agent other than anthracycline derivative, the chemotherapeutic agent is preferably a taxoid, e.g., paclitaxel or doxetaxel. Combined administration herein includes coadministration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in Chemotherapy Service Ed., M. C. Perry, Williams & Wilkins, Baltimore, MD (1992). Administration of the chemotherapeutic agent may precede, or follow, administration of the antibody or may be given simultaneously therewith. The antibody may be combined with an anti-estrogen compound such as tamoxifen or an anti-progesterone such as onapristone (see, EP 616812) in dosages known for such molecules.

(C) Example 1

[0115]

... anti-ErbB2 monoclonal antibody The anti-ErbB2 IgG_1 kappa murine monoclonal antibody 4D5, specific for the extracellular domain of ErbB2, was produced as described in Fendly et al., Cancer Research 50: 1550-1558 (1990) and US Patent 5,677,171 issued October 14, 1997. ...

[0116]

A humanized version of the murine 4D5 antibody (HERCEPTIN (registered trademark)) was engineered by inserting the complementarity determining regions of the murine 4D5 antibody into the framework of a consensus human immunoglobulin IgG_1 (IgG_1) (Carter et al., Proc. Natl. Acad Sci. USA 89: 4285-4289 [1992]; and US Patent No. 5,821,337 issued October 13, 1998). The resulting humanized anti-ErbB2 monoclonal antibody has high affinity for $p185^{HER2}$ (Dillohiation constant [K_d] = 0.1 nmol/L), markedly inhibits, in vitro and in human xenografts, the growth of breast cancer cells that contain high levels of $p185^{HER2}$, induces antibody dependent cellular cytotoxicity (ADCC), and has been found clinically active, as a single agent, in patients with ErbB2-overexpressing metastatic breast cancers that had received

extensive prior therapy.

[0117]

HERCEPTIN (registered trademark) is produced by a genetically engineered Chinese hamster ovary (CHO) cell line, grown in large scale, that secretes the antibody into the culture medium. The antibody is purified from the CHO culture media using chromatographic and filtration methods. Each lot of antibody used is assayed to verify identity, purity, and potency, as well as to meet Food and Drug Administration requirements for sterility and safety.

Patients with primary breast tumor presentation characterized by overexpression of the ErbB2 (HER2) oncogene [2+ to 3+ as determined by immunohistochemistry or fluorescence in situ hybridization (FISH)] are treated herein. Tumor expression of ErbB2 can be determined by immunohistochemical analysis, as previously described (Slamon et al., Science 235: 177-182 [1987]; Slamon et al., Science 244: 707-712 [1989]), of a set of thin sections prepared from the patient's paraffin-archived tumor blocks. Tumors are considered to overexpress ErbB2 if at least 25% of tumor cells exhibit characteristic membrane staining for ErbB2.

[0118]

Patients are first treated with HERCEPTIN for 8-24 weeks, optionally in combination with paclitaxel (TAXOL (registered trademark)), in order to reduce the size of, or eliminate, the tumor prior to surgery. On day 0, a 4 mg/kg dose of HERCEPTIN (registered trademark) is administered intravenously, over a 90-minute period. Beginning on day 7, patients receive weekly administration of 2 mg/kg antibody (iv) over a 90-minute period. Patients may further receive paclitaxel (TAXOL(registered trademark)). The initial dose of the HERCEPTIN(registered trademark) antibody precedes the first cycle of the chemotherapy regimen by 24 hours. Subsequent doses of the antibody are given immediately before chemotherapy administration, if the initial dose of the antibody is well tolerated. If the first dose of the antibody is not well tolerated, subsequent infusions continue to precede chemotherapy administration by 24 hours. Paclitaxel (TAXOL(registered trademark)) is given at a dose of 175 mg/m^2 over 3 hours by intravenous administration. All patients receiving paclitaxel are premedicated with dexamethasone (or its equivalent) 20 mg x 2, administered orally 12 and 6 hours prior to paclitaxel; diphenhydramine (or its equivalent) 50 mg, iv, administered 30 minutes prior to paclitaxel; and dimetidine (or another H2 blocker) 300 mg, iv, administered 30 minutes prior to paclitaxel. After the above therapy, classical measures of response may be evaluated immediately prior to surgery; i.e., the sum of the products

of the crossdimensional diameter of any tumor nodules under observation.

Following therapy as described above, the tumor is surgically removed according to standard surgical procedures; lumpectomy or mastectomy. Pathological response may be evaluated at this stage.

[0119]

After surgery, the patient is treated with HERCEPTIN(registered trademark), optionally in combination with paclitaxel (TAXOL(registered trademark)), in order to reduce the likelihood of disease recurrence. On day 0, a 4 mg/kg dose of HERCEPTIN (registered trademark) is administered intravenously, over a 90-minute period. Beginning on day 7, patients receive weekly administration of 2 mg/kg antibody (iv) over a 90-minute period. Therapy with HERCEPTIN (registered trademark) is continued for one year. Patients may further receive paclitaxel (TAXOL(registered trademark)) for 6-24 weeks. The initial dose of the HERCEPTIN (registered trademark) antibody precedes the first cycle of the chemotherapy regimen by 24 hours. Subsequent doses of the antibody are given immediately before chemotherapy administration, if the initial dose of the antibody is well tolerated. If the first dose of the antibody is not well tolerated, subsequent infusions continue to precede chemotherapy administration by 24 hours. Paclitaxel (TAXOL(registered trademark)) is given at a dose of 175 mg/m^2 over 3 hours by intravenous administration. All patients receiving paclitaxel are premedicated as described above.

Patients treated according to the above therapeutic regimen will display improved overall survival and/or reduced time to tumor progression (TTP).

(2) According to the aforesaid item (1), the patented inventions are set forth as below.

A It had been known before the priority date that the human erbB2 (HER2) gene encoding a transmembrane glycoprotein receptor (p185HER2) was overexpressed in about 25% to 30% of human breast cancer ([0002]).

It had been known to a person ordinarily skilled in the art that a humanized 4D5 anti-ErbB2 antibody against human ErbB2 (HER2) protein, which was a protein product of human erbB2 (HER2) gene (hereinafter referred to as "anti-HER2 antibody", but in some cases referred to as "trastuzumab", "Trastuzumab", or "Herceptin") was effective for patients with metastatic breast cancer overexpressing ErbB2 (HER2) who had previously undergone a broad anticancer therapy ([0011]), and had an effect of promoting activity of paclitaxel (taxol) and doxorubicin on breast cancer xenografts in nude mice injected with BT-474 human breast adenocarcinoma

cells, which express high levels of HER2 ([0012]).

B The patent invention relates to a pharmaceutical for treating a human patient diagnosed with breast tumor that overexpresses ErbB2 (HER2) protein; this pharmaceutical comprises a therapeutically effective amount of anti-HER2 antibody, and has a technical feature of using three-step therapy of the following items (A) to (C) ([0013], [0105]).

(A) First stage

A therapeutically effective amount of anti-HER2 antibody is administered to the patient in order to reduce the size of, or eliminate, the tumor (or tumors) in the patient prior to surgery. One or more chemotherapeutic agents are optionally further administered prior to surgery.

(B) Second stage

A tumor is surgically removed according to standard surgical procedures (e.g. lumpectomy or mastectomy).

(C) Third stage

A therapeutically effective amount of anti-HER2 antibody or at least one chemical agent is administered to patients to reduce the possibility of the recurrence of diseases.

C Examples of the corrected description describe a method for the production of anti-HER2 antibody ([0115]), and disclose that the antibody markedly inhibits, in vitro and in human xenografts, the growth of breast cancer cells that contain high levels of $p185^{HER2}$, induces antibody dependent cellular cytotoxicity (ADCC), and is clinically active, as a single agent, in patients with ErbB2 (HER2)-overexpressing metastatic breast cancers that had received extensive prior therapy ([0116]).

Further, it describes the effects caused by applying anti-HER2 antibody to patients before surgery optionally in combination with paclitaxel (TAXOL (registered trademark)) as in the following: "Patients treated according to the above therapeutic regimen will display improved overall survival and/or reduced time to tumor progression (TTP)." ([0119]).

2 Common technical knowledge as of the priority date

(1) Anti-HER2 antibody

A Exhibit Ko 1 (Defendant, package insert of HERCEPTIN (registered trademark) approved in the U.S., September 25, 1998), the publication distributed prior to the priority date, has the following descriptions (the description and cited part are shown by the translation of Exhibit Hei 7; the line number of cited part is the line number from which Tables and their explanation were excluded):

(A) Title

"HERCEPTIN(registered trademark) trastuzumab" (page 1, lines 1 to 2)

(B) WARNING

"Cardiomyopathy:

HERCEPTIN administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with HERCEPTIN. Discontinuation of HERCEPTIN treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who received HERCEPTIN in combination with anthracyclines and cyclophosphamide. (See WARNINGS)" (page 1, lines 4 to 9)

(C) DESCRIPTION

"HERCEPTIN (Trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2." (page 1, lines 11 to 15) "HERCEPTIN is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each vial of HERCEPTIN contains 440 mg Trastuzumab, 9.9 mg L-histidineHCl, 6.4 mg L-histidine, 400 mg alpha, alpha-trehalose dihydrate, and 1.8 mg polysorbate 20, USP." (page 1, lines 19 to 22)

(D) CLINICAL PHARMACOLOGY - General

"The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185kDa, which is structurally related to the epidermal growth factor. HER2 protein overexpression is observed in 25%-30% of early stage breast cancers. HER2 protein overexpression can be determined using an immunohistochemistry-based assessment of fixed tumor blocks.

Trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC). In vitro, HERCEPTIN mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2." (page 1, line 27 to page 2, line 4)

(E) CLINICAL PHARMACOLOGY - Pharmacokinetics

"The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg Herceptin once weekly demonstrated dose-dependent pharmacokinetics." (page 2, lines 6 to 7)

"Mean serum trough concentrations of Trastuzumab, when administered in combination with paclitaxel, were consistently elevated approximately 1.5-fold as compared with serum concentrations of Trastuzumab used in combination with anthracycline plus cyclophosphamide." (page 2, lines 25 to 27)

(F) CLINICAL STUDIES

"The safety and efficacy of HERCEPTIN were studied in a randomized, controlled clinical trial in combination with chemotherapy (469 patients) and an open-label single agent clinical trial (222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2+ or 3+ levels of overexpression (based on a 0-3+ scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

A multicenter, randomized, controlled clinical trial was conducted in 469 patients with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Patients were randomized to receive chemotherapy alone or in combination with HERCEPTIN given intravenously as a 4 mg/kg loading dose followed by weekly doses of HERCEPTIN at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles)." (page 2, line 33 to page 3, line 10)

"Compared with patients randomized to chemotherapy alone, the patients randomized to HERCEPTIN and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a higher one-year survival rate. (See Table 1.) These treatment effects were observed both in patients who received HERCEPTIN plus paclitaxel and in those who received HERCEPTIN plus AC; however, the magnitude of the effects was greater in the paclitaxel subgroup. The degree of HER2 overexpression was a predictor of treatment effect. (See CLINICAL STUDIES: HER2 protein overexpression.)" (page 3, lines 14 to 20)

Table 1
Phase III Clinical effect of first line of treatment

	Combination effect		Paclitaxel subgroup		AC subgroup	
	Herceptin + All chemotherapies (n = 235)	All chemotherapies (n = 234)	Herceptin + Paclitaxel (n = 92)	Paclitaxel (n = 96)	Herceptin + AC[a] (n = 143)	AC (n = 138)
Primary endpoints						
Disease progression [b, c]						
Median (month)	7.2	4.5	6.7	2.5	7.6	5.7
95% confidence interval	6.9, 8.2	4.3, 4.9	5.2, 9.9	2.0, 4.3	7.2, 9.1	4.6, 7.1
p value (log value)	<0.0001		<0.0001		0.002	
Secondary endpoints						
Overall response rate [b]						
Proportion (percent)	45	29	38	15	50	38
95% confidence interval	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p value (χ2-)	<0.001		<0.001		0.10	
Duration of response [b, c]						
Median (month)	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% fractile	5.5, 14.8	3.9, 8.5	5.1, 11.0	3.7, 7.4	5.8, 14.8	4.5, 8.5
One-year survival [c]						
Percent survival	79	68	73	61	83	73
95% confidence interval	74, 84	62, 74	66, 80	51, 71	77, 89	66, 82
p value (Z-test)	<0.01		0.08		0.04	

[a] AC = anthracycline (doxorubicin or epirubicin) and cyclophosphamide
[b] Evaluation by independent members for response evaluation
[c] Kaplan-Meier method

"HER2 protein overexpression

Relationship to Response: in the clinical studies described, patient eligibility was determined by testing tumor specimens for overexpression of HER2 protein. Specimens were tested with a research-use-only immunohistochemical assay (referred to as the Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Data from both efficacy trials suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+). (See Table 2.)." (page 4, lines 10 to 16)

(G) Indications and Usage

"HERCEPTIN as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. HERCEPTIN in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. HERCEPTIN should only be used in patients whose tumors have HER2 protein overexpression" (page 5,

lines 16 to 20)

(H) WARNING

"Cardiotoxicity:

... Patients receiving HERCEPTIN should undergo frequent monitoring for deteriorating cardiac function.

The probability of cardiac dysfunction was highest in patients who received HERCEPTIN concurrently with anthracyclines. ..." (page 6, lines 1 to 15)

(I) Supplying method

"HERCEPTIN is supplied as a lyophilized, sterile powder containing 440 mg Trastuzumab per vial under vacuum." (page 11, lines 25 to 26)

B Exhibit Ko 2 (Vincente Valero, "Future Direction of Neoadjuvant Therapy for Breast Cancer", Seminars in Oncology Vol 25 No 2 Suppl 3 pp 36-41, April 1998), a publication distributed before the priority date, has the following description (the description and cited part are shown by the translation attached to Exhibit Ko 2 [Whole translation]):

(A) Title

"Future trend of neoadjuvant therapy for breast cancer" (page 1, line 1)

(B) Introduction

"A primary chemotherapy or neoadjuvant chemotherapy consists of chemotherapy for patients suffering from breast cancer that is implemented prior to a limitative local domain therapy. One major advantage of this approach is that there is possibility of an effective postoperative therapy being selectable by determining a biological response against a specific chemotherapy or a regimen. This approach has been first introduced into patients suffering from a locally-advanced breast cancer (LABC), and has drastically changed the treatment of LABC over the past two decades. Primary chemotherapy has become an essential part in multidisciplinary approach of LABC. For these patients, it allows for the increase in disease-free survival, the extension of total survival, and breast conservation surgery. A major goal of primary chemotherapy excludes distant micrometastases. In addition, it was used for local treatment in these patients suffering from inoperable tumor to improve local region control." (page 1, lines 13 to 22)

(C) Multidisciplinary approach

"In the early 1970s, a strong trend of generating distant micrometastases was observed in early stage breast cancer. Systemically combined chemotherapy has been introduced as a primary therapy for these patients on the basis of this knowledge and poor prognosis of LABC patients. Tumor blood circulatory system is unchanged

by surgery or radiation therapy. Thus early initiation of systemic treatment is advantageous. Resistant clone would have almost no opportunity to occur. Furthermore, oncologists have an opportunity to determine the efficacy of systemic treatment in the living body. If systemic therapy is ineffective, oncologists cease the ineffective therapy, avoid unnecessary toxicity, and initiate an alternative form of systemic therapy. Furthermore, the regression of tumor stage allows for breast conservation surgery, and makes inoperable tumors operable." (page 2, lines 2 to 10)

"Until recently, it has been unknown as to whether the timing of systemic therapy (primary versus adjuvant) might change the ratio of benefit and risk in patients suffering from operable breast cancer. However, a large-scale randomized clinical test has demonstrated that primary chemotherapy is effective comparable to postoperative chemotherapy (disease-free survival and overall survival), but results in a higher breast preservation rate. After primary chemotherapy, primary tumor might be completely diminished or its size might be decreased." (page 2, lines 25 to 29)

(D) New strategy

"One study trend for improving the survival of patients suffering from high-risk breast cancers including LABC is an increase of dose amount of primary chemotherapy or postoperative chemotherapy in the presence or absence of blood-forming support." (page 2, lines 41 to 42)

(E) New chemotherapeutic agents

"Taxanes such as paclitaxel and docetaxel are new antimicrotubule agents reversibly and specifically binding to beta-subunit of tubulin. They have a unique action mechanism on cells: promotion of stable tubulin polymerization to a bundle of microtubules; and inhibition of tubulin depolymerization. These effects inhibit the reconstruction of skeleton/network of microtubules necessary for mitosis and other important cell functions. Taxanes block cells in G_2/M stage of cell cycle." (page 3, lines 28 to 33)

"Paclitaxel demonstrated significant antitumor activity against metastatic breast cancer even in patients who suffered from anthracyclin resistant tumor. A single agent of paclitaxel provided an objective response rate of 6% to 48% in preliminarily-treated patients, and 32% to 62% for primary therapy. The optimal schedule period and doses of paclitaxel is still unknown ... A preliminary result of phase III test in which paclitaxel was compared with cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone demonstrated a similar level of objective response rate and a median value of overall survival, and showed a better score for quality of life.

A preliminary result of combined chemotherapy in combination with paclitaxel

seems to be promising. ... The phase II test combines paclitaxel with cyclophosphamide, mitoxantrone, carboplatin, vinorelbine, and cisplatin. The preliminary results are very encouraging, as they suggest synergistic effects." (page 3, line 35 to page 4, line 12)

"a semisynthetic compound of decetaxel prepared from a cell toxicity-free precursor, 10-deacetylbaccatins III, has several advantages over paclitaxel. In many tumor models, docetaxel demonstrates significant preclinical activity. Similarly to cisplatin, cyclophosphamide, and doxorubicin, it shows a higher celltoxic activity compared to paclitaxel. ...

... Two randomized international multicenter phase III tests were designed to confirm the above promising results by comparing docetaxel with established agents (doxorubicin and mitomycin-C plus vinblastine). The final study result is very encouraging: docetaxel provided a significantly higher objective response rate (48% v 33%; P=.008) compared to doxorubicin and a significantly quicker time to a first response (12 weeks v 23 weeks: P=.007). Docetaxel provided a significantly high objective response rate (30% v 12% :P=.001) and a significantly longer timer to progression (19 weeks v 11 weeks; P=.0001) and a significantly longer survival median value (11.4 months v 8.7 months: P=.0097) in comparative tests with mitomycin and vinblastine. It seems that a preliminary result of combined chemotherapy in combination with docetaxel is very promising. A combination of docetaxel and doxorubicin shows a significant activity without increasing the occurrence of cardiac toxicity.

In patients with early-stage breast cancer and LABC, a role of docetaxel in a single drug or a combined drug has been currently almost determined in some studies. The preliminary results of initial neoadjuvant studies are recently shown. LABC patients initially received docetaxel (100 mg/m^2) for 4 cycles, and underwent surgery, and received doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) for 4 cycles. Clinically objective response rate was 83%. In the other study implemented in The University of Texas MD Anderson Cancer Center, neoadjuvant therapy patients initially received doxorubicin (60 mg/m^2 over 15 minutes) and docetaxel (600 mg/m^2 over 1 hour) for 4 cycles, and underwent surgery, and received cyclophosphamide, methotrexate, and 5-fluorouracil for 6 cycles. ..." (page 4, line 22 to page 5, line 9)

(F) Biologically - genetically new therapy

"Owing to a better understanding of molecular biology of cells, new targets are identified for treatment. These targets include growth factor and growth factor receptor. The amplification of normal gene and the overexpression of normal gene

(e.g. overexpression) or the activity of cancer gene might result in the overexpression of growth factor or growth factor receptor. As long as a growth factor receptor is not intact, a growth factor cannot stimulate cell fission, and thus these receptors become a new target for treatment. One approach is to make an antibody that blocks a receptor. Growth factor receptor frequently overexpressed in breast cancers includes epidermal growth factor receptor and HER-2/neu receptor. A promising result of clinical test of monoclonal antibody against HER-2/neu receptor has been recently presented. In a phase II test, 46 patients with stage IV breast cancer and positive expression of HER-2/neu were treated intravenously with 250 mg HER-2/neu antibody over 90 minutes, and then treated with 100 mg weekly for 10 weeks. The target response rate was 12%, and the therapy was quite allowable. A test in progress combines a recombinant human HER2 monoclonal antibody with other agents such as doxorubicin, cisplatin, and paclitaxel. Further, a randomized Phase III test targets doxorubicin and cyclophosphamide in combination with or not in combination with recombinant human HER2 monoclonal antibody as a first-line treatment for metastatic disease. The role of these new strategies in combination with primary chemotherapy should be evaluated by early-stage breast cancer patients." (page 6, lines 2 to 19)

(G) Conclusion

"In summary, a multidisciplinary approach is becoming a treatment to be selected for patients with LABC, and becoming an essential part of a treatment of patients with early-stage breast cancer (stage II). The multidisciplinary approach provides patients suffering from LABC with appropriate local control, the possibility of breast conservation therapy, and the increases in survival rate. It provides a similar survival rate to that for adjuvant therapy in patients with early-stage breast cancer. Several problems still remain unsolved at present. We need to develop a better biological marker for determining the aggression of the disease. The best chemotherapy regimen has not yet been defined. The latest information suggests that the best result may be obtained by a regimen including doxorubicin. The role of hormone therapy is not defined; therefore, a clinical test should be designed so as to establish a value to add hormone therapy to a multidisciplinary approach. It is indefinite as to what the optimal treatment order should be after primary chemotherapy, whether one or two local treatment modalities are necessary, or whether optional or different postoperative chemotherapy is also necessary. The optimal order determination using the optimal local treatment (or plural local treatment) and combined systemic therapy should be defined. The outcome in patients of this group may be further improved by additionally improving these

strategies, including the selection of postoperative chemotherapy on the basis of the response against induction chemotherapy.

The role of high dose chemotherapy as a therapy for promoting an effect of primary chemotherapy is about to be evaluated in patients (patients with metastatic axillary nodes beyond 4) at a high risk of the recurrence after primary chemotherapy. Clinical tests with a plurality of new and effective cell damaging agents including docetaxel, paclitaxel, and vinorelbine is about to start. Monoclonal antibodies against specific tumor antigen, cancer gene, growth factor, or growth factor receptor reveal a possibility of innovative and potentially more selective treatment. Clinical investigation during the next decade will establish the role of these new modalities in the overall management of patients with locally-advanced breast cancer." (page 6, line 21 to page 7, line 1)

C Exhibit Ko 3 (EDITH A. PEREZ, "Paclitaxel in Breast Cancer", The Oncologist 1998; 3: pp 373-389, 1998), a publication distributed prior to the priority date of the subject patent, has the following descriptions (the description and cited part are shown by the translation attached to Exhibit Ko 3 and a translation of Exhibit Hei 6-2.):

(A) Abstract

"Paclitaxel has emerged as an important agent in the treatment of breast cancer. The efficacy and tolerability of this agent, as well as its lack of cross-resistance with anthracyclines, have spurred intensive clinical investigation worldwide. ... Weekly moderate dose paclitaxel administration is also generating much interest, given the high relative dose intensity and dose density delivered, yet very modest myelosuppression and manageable neurotoxicity observed.

As first-line therapy in metastatic disease, multiple studies have documented overall response rates in the range of 30%-60%. As a second-line or a salvage therapy in metastatic patients, paclitaxel generally affords an overall response rate of 20%-40%, even in anthracycline-resistant patients.

The novel mechanism of action and manageable toxicity of paclitaxel has led to successful incorporation into combination chemotherapy regimens. The combination of paclitaxel and doxorubicin has been the most extensively studied, with the role of this regimen continuing to evolve. Other combination regimens that appear to hold substantial promise as first-line metastatic treatment are paclitaxel with carboplatin and paclitaxel with trastuzumab (anti-HER2 antibody). The favorable results obtained in the metastatic setting have prompted phase II and phase III investigations of paclitaxel in the adjuvant and neoadjuvant settings. ...

Current investigations with paclitaxel will continue to optimize the role of this agent in the treatment of early- and advanced-stage breast cancer, addressing not only response rates but also survival and quality-of-life issues. The use of paclitaxel on a weekly schedule or in combination with new therapeutic modalities, such as monoclonal antibodies, is also receiving much attention. While it is clear that paclitaxel is a very active agent in the treatment of breast cancer, it is hoped that these innovative trials will further maximize the potential of this agent in patients with breast cancer." (Exhibit Hei 6-2, page 1, line 2 to page 2, line 1)

(B) Introduction

"The role of paclitaxel is being investigated in settings ranging from first-line, second-line, and salvage therapy for metastatic disease, as well as adjuvant and neoadjuvant treatment." (Exhibit Hei 6-2, page 2, lines 4 to 6)

(C) METASTATIC BREAST CANCER - Single-Agent Therapy

"Since chemotherapy in metastatic breast cancer patients remains palliative, both response and tolerability are important considerations in evaluating new agents. Paclitaxel has been shown to achieve comparatively high response rates with an acceptable toxicity profile." (Exhibit Hei 6-2, page 2, lines 13 to 16)

(D) METASTATIC BREAST CANCER - Combination Chemotherapy

"Combination chemotherapy is the standard approach to the treatment of breast cancer. Multidrug regimens have generally resulted in higher complete and overall response rates, with improvements in response durations. The novel mechanism of action of paclitaxel, its demonstrated single-agent activity, and its manageable toxicity profile make it an attractive candidate for inclusion in combination chemotherapy regimens." (Exhibit Hei 6-2, page 2, lines 20 to 24)

(E) METASTATIC BREAST CANCER - Combination Chemotherapy / Monoclonal Antibody Therapy

"Paclitaxel and Anti-HER2 Antibody

A trial that has recently generated much notice is the combination of the anti-HER2 antibody, trastuzumab (Herceptin(registered trademark)), with chemotherapy in patients with metastatic breast cancer overexpressing the HER2 receptor. In this multinational controlled phase III trial, patients were treated with either combination doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 with cyclophosphamide 600 mg/m^2, or with paclitaxel 175 mg/m^2 by 3-h infusion if they had already received adjuvant anthracycline therapy.

Patients in each group were then stratified to receive anti-HER2 antibody therapy in addition to chemotherapy. A total of 469 patients were enrolled. The

overall response rate to all chemotherapy with anti-HER2 antibody was 48%, with a median time-to-tumor progression of 7.6 months, higher than that of chemotherapy without the antibody (overall response 32%, median time-to-tumor progression 4.6 months, p = 0.001). Specifically for paclitaxel, the overall response rate with antibody was 42%, with a time-to-tumor progression of 6.9 months, statistically greater than that for paclitaxel alone, which had an overall response rate of 16% (p = 0.001) and a three-month median time-to-tumor progression (p = 0.0001)." (Exhibit Hei 6-2, page 2, line 29 to page 3, line 11)

"it was suggested that future studies administering concurrent chemoimmunotherapy with anti-HER2 antibody focus on paclitaxel-based therapy. Currently, clinical trials of paclitaxel and anti-HER2 antibody are being developed for patients with locally-advanced breast cancer, as well as trials of doxorubicin/cyclophosphamide with dexrazoxane and anti-HER2 antibody. Along with these agents, combination antibody therapy with other drugs, such as carboplatin, may be warranted. It is clear that evaluation of chemotherapy/antibody trials in breast cancer will be a priority in the coming years." (Translation, page 1, lines 20 to 21, Exhibit Hei 6-2, page 3, lines 13 to 18)

(F) PACLITAXEL IN ADJUVANT THERAPY

"While the majority of breast cancer patients present with disease confined to the breast, many subsequently relapse and eventually succumb to metastatic disease. Accordingly, a major goal of adjuvant chemotherapy is elimination of micrometastatic disease likely to be present at the time of initial diagnosis. The importance of adjuvant treatment for breast cancer has been widely accepted since the 1970s. Further evidence supporting this view was a 1992 worldwide meta-analysis of 10-year follow-up results from randomized trials, which revealed significant improvements in disease-free and overall survival in patients receiving adjuvant chemotherapy." (Exhibit Hei 6-2, page 3, lines 21 to 27)

"Neoadjuvant Clinical Trials

Novel chemotherapeutic strategies that prove successful in the metastatic and adjuvant settings may potentially also find application in neoadjuvant treatment. By diminishing primary tumor size, neoadjuvant therapy may allow a patient to undergo more conservative surgery or even render an otherwise inoperable patient operable. Also, therapy may impact local and distant relapse. Neoadjuvant paclitaxel treatment is under study in a number of clinical trials (Table 5)." (Exhibit Hei-6-2, page 4, lines 18 to 24)

"An Austrian multicenter, open-label, dose-escalating phase II trial of

neoadjuvant paclitaxel has been completed. An overall response rate of 61% was observed in patients treated with paclitaxel 250 mg/m^2 for a minimum of four cycles or best response, followed by surgery. Among the 33 study patients, neoadjuvant paclitaxel allowed modified radical mastectomy to be performed in 23 and partial resection in eight. Three of the nine patients originally with T3 disease were able to be downstaged." (Exhibit Hei 6-2, page 4, lines 26 to 32)

(G) Conclusion

"The unique mechanism of action of paclitaxel and its relatively well-tolerated toxicity profile have made it a candidate for combination therapy with other active agents in breast cancer." (Translation, page 2, lines 10 to 11)

"Finally, the addition of paclitaxel to anti-HER2 antibody therapy has resulted in much interest over the response and tolerability of this combination. This trial not only demonstrates the improved efficacy of combination antibody therapy with traditional chemotherapy in advanced breast cancer, it heralds the arrival of a new and anxiously awaited class of anticancer agents. Much activity in this area is expected in the coming years." (Translation, page 2, lines 13 to 17)

D Exhibit Hei 2, a publication distributed before the priority date, (Masashi ANDO, Ryo WATANABE, "Application of HER^2/neu for the treatment", Blood, Immunology and Tumor, Vol. 4, No. 2, pages 65 to 70, April 1999) has the following description (the line number of cited part is the line number from which Tables and their explanation were excluded.):

(A) Key Sentences

"[i] HER2 protein has a tyrosine kinase activity in intracellular portion and is involved with the adjustment of cellular growth with overexpression in about 25 to 30% of breast cancers. Antibody of HER2 protein suppresses the growth of breast cancer cell with HRE2 [Court decision's note: it is recognized as a typo of "HER2".] protein overexpression.

[ii] Trastuzumab combines an antigen recognition site of mouse antibody against an extracellular component of HER2 protein and human IgG_1 by gene recombination. Its clinical introduction is actively promoted as a breast cancer treatment agent.

[iii] The response rate of Trastuzumab against metastatic breast cancer with HER2 protein overexpression and previously treated history was about 11 to 15%, and about 20% for initial therapy.

[iv] A combination of Trastuzumab with adriamycin or paclitaxel for metastatic breast cancer with HER2 protein overexpression has excellent time-to-tumor

progression, response rate, and 1-year survival rate compared to a single anticancer agent.

[v] Major adverse events in association with Trastuzumab administration may include pain, general malaise, fever, chill, nausea, cephalea, diarrhea, and asitia. In combination with an anticancer agent (particularly adriamycin), the development of cardiac depression was promoted." (page 65)

(B) Introduction

"Cancer gene HER^2/neu encodes 185kDa protein with a receptor structure on cell surface membrane. HER2 protein has tyrosine kinase activity in intracellular portion, and is involved with the adjustment of cellular growth. The amplification of HER^2/neu and the overexpression of HER2 protein are observed in about 25 to 30% of breast cancers. Recently, immunohistological dyeing of fixed sample of tumor tissues facilitate the detection of overexpression. In an experimental system in-vitro or using xenograft, it is reported that monoclonal antibody against HER2 protein suppresses the growth of breast cancer cells in which the protein overexpresses. Further, this antibody shows antibody-dependent cellular cytotoxicity against tumor cells in which HER2 protein is overexpressed in a living body. An application of this antibody for treatment has been considered with an expectation of suppressing the growth. Herceptin (registered trademark) (Trastuzumab) is a monoclonal antibody developed by Genentech in the United States that combines an antigen recognition site of the mouse antibody 4D5 against an extracellular component of HER2 protein and human IgG_1 by gene recombination. Humanization decreases the antigenecity of the antibody itself, and a clinical introduction has been positively promoted." (page 65, left column, line 2 to page 66, left column, line 3)

(C) Clinical test of single agent against breast cancer

"Compared with a response rate of a test directed to the cases after implementation of chemotherapy, it is suggested that Trastuzumab has no cross-tolerance with anticancer agents." (page 66, the right column, lines 29 to 31)

(D) Combined therapy between Trastuzumab and anticancer agents

"An in vitro experiment shows that an antitumor effect is promoted by the combination of anti-HER2 antibody and anticancer agents (adriamycin, paclitaxel, cisplatin, etc.) for tumor cells in which HER2 protein is overexpressed. In view of these results, a clinical test was implemented for a combination therapy with an anticancer agent. For untreated metastatic breast cancer with HER2 protein overexpression, AC therapy was implemented at an interval of 3 weeks by 6 courses (administer adriamycin 60 mg/m^2 or epirubicin 75 mg/m^2/cyclophosphamide 600

mg/m^2 at Day 1) in a case where adriamycin was not implemented as an adjuvant therapy, and paclitaxel 175 mg/m^2/3 hour infusion was administered at an interval of 3 weeks by 6 courses in a case where adriamycin was implemented as an adjuvant therapy. Furthermore, each treatment group was randomized into a group subjected to Trastuzumab simultaneous to chemotherapy (loading dose: 4 mg/kg, maintenance dose: 2 mg/kg once daily) and a group subjected to a single chemotherapy (Table 1). A group subjected to paclitaxel often has an adverse prognostic factor compared to an AC therapy group. A combination group has excellent in time-to-tumor progression, response rate, and 1-year survival rate compared to a single chemotherapy group. In particular, a combination effect was significant in a group subjected to paclitaxel.

In phase II test combining cisplatin, for metastatic breast cancer with chemotherapy resistant HER^2/neu protein overexpression, Trastuzumab was administered with a loading dose of 250 mg/body (day 1) and a maintenance dose of 100 mg/body 9 times weekly, and 75 mg/m^2 cisplatin was coadministered at days 1, 29, and 57. Response rate of 37 cases was PR 24.3%, and median response durations were 5.3 months. Response rate of cisplatin against chemotherapy-resistant breast cancer was 7%, which suggests the promotion of antitumor effects due to the combination with anti-HER2 antibody." (page 66, right column, line 33 to page 67, right column, line 6)

(E) Relationship between the degree of HER2 protein expression and antitumor effect of antibody

"In a clinical test by anti-HER2 antibody, the presence or absence of HER2 protein overexpression was determined by immunohistological dyeing of tumor tissues in determining eligibility. A degree of dyeing was ranked as four stages of 0, 1+, 2+, and 3+, and 2+ and 3+ are determined as overexpression. In the aforesaid Phase II test of single agent Trastuzumab and the test combined with an anticancer agent, a consideration was given to a correlation of a degree of HER2 protein overexpression with an antitumor effect (Table 2).

According to these results, there was a trend showing that cases with a stronger expression of HER2 protein were more excellent in both antitumor effect and time-to-tumor progression in both cases of single agent administration and coadministration with an anticancer agent." (page 67, right column, line 9 to page 69, left column, line 3)

(F) Adverse event in association with Trastuzumab administration

"in adverse events recognized in association with Trastuzumab administration, a focused issue was cardiac toxicity. Congestive heart failure occurred. In a phase

II test with a single agent Trastuzumab, 10 out of 212 cases underwent 10% or more decrease in cardiac output compared to before treatment. Eight cases had symptoms such as breathing trouble, and four cases died. Further, the administration of Trastuzumab was continued for 8 cases. In combination test with anticancer agent, a group with a combination of Trastuzumab and anticancer agent frequently showed a decrease in cardiac function (Table 3). Seidman et al. considered cases with decrease in cardiac function that was observed in the previous clinical tests of Trastuzumab. Cases with 10% or more decrease in cardiac output before treatment totaled 89 cases out of 977 cases, which was frequently higher in combination with AC therapy. The clinical image was analogous to the decrease in cardiac function that occurred after the administration of anthracycline-based anticancer agents. Responding to the treatment against common heart failure, 2% or less of cases resulted in sustained serious cardiac failure or death. Further, the administration of Trastuzumab was continued for 80% of the cases showing cardiac depression. At present, the mechanism of causing the decrease in cardiac function is unknown." (page 69, left column, line 29 to right column, line 12)

E According to the aforesaid A to D, it is recognized that a person ordinarily skilled in the art had the following common technical knowledge for anti-HER2 antibody as of the priority date (May 14, 1999).

(A) Herceptin, a pharmaceutical with an active ingredient of anti-HER2 antibody of Trastuzumab, was approved in the United States on September 25, 1998 (Exhibit Ko 7).

The indications for HERCEPTIN are allegedly patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. The indications do not include patients with operable breast cancer (aforesaid item A(G)).

(B) HER2 protein is involved with cell growth modulation, and its overexpression is observed in 25% to 30% of early stage breast cancers (aforesaid item A(D), D(A)(B)).

Anti HER2 antibody binds to an extracellular area of HER2 protein to suppress the growth of breast cancer cells that overexpress HER2 protein and show antibody-dependent cellular cytotoxicity (ADCC) in a living body (aforesaid item A(D), D(A)(B)). Antibody-dependent cellular cytotoxicity is an action of immune cells to kill and damage target cells to which an antibody binds (Exhibit Hei 8).

(C) When anti-HER2 antibody was coadministered with a chemotherapeutic agent of ([i] paclitaxel, [ii] anthracycline [doxorubicin (adriamycin [Exhibit Hei 3]) or

epirubicin] and cyclophosphamide, [iii] cisplatin) to metastatic breast cancer patients with tumors that overexpress HER2 protein, a time-to-tumor progression is prolonged as compared to patients in which the chemotherapeutic agent was solely administered, the overall response rate (ORR) was improved, the median of the response period was prolonged, one-year survival rate was improved, and antitumor effect was promoted (aforesaid item A(F), C(E), D(A)(D)). Particularly in paclitaxel, the effect of the combination of anti-HER2 antibodies was significant (aforesaid A(F), C(E), D(D)).

(D) In a clinical test of anti-HER2 antibody, there was a trend showing that cases with a stronger expression of HER2 protein were more excellent in both antitumor effect and time-to-tumor progression in both cases of single agent administration and coadministration with a chemotherapeutic agent (aforesaid A(F), D(E)). HERCEPTIN should be used only in patients whose tumors have HER2 protein overexpression (aforesaid item A(G)).

(E) Adverse events of the administration of anti-HER2 antibody include cardiac toxicity. The administration can result in ventricular dysfunction and congestive heart failure. Patients who were coadministered with a chemotherapeutic agent underwent the decrease in cardiac function in many cases, which was frequent in the combination with anthracycline (adriamycin or epirubicin) and cyclophosphamide. Responding to the treatment against common heart failure, 2% or less of cases resulted in sustained serious cardiac failure or death. (aforesaid A(B)(H), D(A)(F))

(2) Therapy of operable breast cancer

A Exhibit Ko 14 ("Neoadjuvant Chemotherapy" "Clinical of breast cancer", Vol. 8, No. 2, pages 181 to 197, June 1993), a publication distributed before the priority date, has the following description (the line number of the cited part is the line number from which Tables and their explanation were excluded.):

(A) Introduction

"The term 'neoadjuvant chemotherapy (NACT)' was coined by Frei on 1982 as a new therapeutic strategy. Previously, this therapeutic strategy was started for the field of orthopedics or head and neck neoplasm in childhood neoplasm. NACT means chemotherapy that precedes local therapy (surgery, radiation therapy) against primary solid tumor, and is actually implemented as a part of a multidisciplinary approach, and it is often the case that the local therapy is followed by adjuvant chemotherapy (ACT). ...

... In a case where a radical local therapy is implemented in a solid tumor, it is believed that the remedy is possible if a potential remaining tumor cell number is

lowered to a range under the control by a host (10^{3-4} cells or less), whereas it eventually leads to the recurrence if tumor cells remain beyond a limit of the host control (10^{3-4} to 10^{8-9} cells). If the recurrence is frequent as distant metastases from a viewpoint of the recurrence, the tumor is assumed to be a tumor system likely to have already had distant micrometastases at the timing of local therapy; i.e., a tumor system with a strong systemic nature. Thus if one wishes to achieve a curative therapeutic effect, it is essential to remove remaining tumor cells through an effective systemic drug therapy including chemotherapy in addition to local therapy.

On the other hand, the treatment of breast cancer after local therapy results in failure due to the recurrence mostly when it is attributed to the recurrence from distant metastases. ... A proportion of cases where only distant metastases are an initial site of recurrence in recurrent case is 63 to 83%, and reaches about 70 to 80% if simultaneous local recurrence is included. If the date of these reports is considered, it is presumed that the progress of diagnosing technique might even have a possibility of further increasing the proportion of cases where only distant metastases are an initial site of recurrence. As seen above, among solid tumors, breast cancer is supposed to be a tumor with a strong nature of systemic illness. There is a prevailing belief that many cases of breast cancer have micrometastases at the timing of clinical discovery.

From the aforementioned background, it is recognized that local therapies such as surgery and radiation therapy have an insufficient therapeutic effect for relatively earlier-stage breast cancer, and systemic therapy such as postoperative adjuvant chemotherapy and endocrine therapy was introduced. However, the therapeutic result is far from a level that should be satisfied, particularly in locally-advanced breast cancer. The therapeutic effect of NACT is expected as one method for the improvement of therapeutic result. In breast cancer, NACT was introduced as a part of multidisciplinary approach in Milan Cancer institute on 1973 and in the United States M.D. Anderson Hospital on 1974." (page 181, line 19 to page 183, line 6)

(B) The purpose of Neoadjuvant therapy

"A primary goal is the improvement of local control due to the reducing effect of primary tumors. In a case where local therapy (radical surgery, radiation therapy) is difficult, the downstaging of tumor allows for local therapy. In a case where a radical local therapy is feasible, a further conservative local therapy is feasible by further downstaging tumors to minimize postoperative functional, beauty damage. In breast cancer, breast conservation is also a goal.

A second purpose is to start treatment in an earlier stage for systemic

micrometastases, eradicate micrometastases, extend disease-free interval (DFI) and overall survival, and finally improve a cure rate." (page 183, lines 8 to 15)

(C) Current situation of NeoAdjuvant ChemoTherapy

"In breast cancer, NACT was first introduced for the purpose of reducing a progress level of primary tumors as possible and facilitating radical local therapy (surgery, radiation therapy) in a locally-advanced breast cancer. Thereafter, NACT allows for more conservative radical local therapy. As it is shown that the opportunity of breast conservation is increased, it is tried for earlier stage breast cancer of stage I, II. Currently, a clinical study is ongoing for a major purpose of the extension of DFI and overall survival; i.e., the improved cure rate, and the expansion of the opportunity of breast conservation." (page 186, lines 4 to 9)

"Locally-advanced breast cancer is not definitely defined; however, it almost shows a status corresponding to stage III of TNM classification (1987). Besides, the cases classified into stage IV due to local evolution or lymph node metastases are also classified into a locally-advanced breast cancer in some instances" (page 187, lines 2 to 4)

"On the basis of the experience and results of NACT in stage III, this method is about to be introduced for earlier stages of stage I, II. ... The goal is to improve local control and cure rate similar to stage III. In earlier stage breast cancer, the expectation for the expansion of opportunity of breast conservation is further stronger. Used agent and regimen are the same as stage III; however, the frequency of administration of NACT tends to be designed even higher. Thus it seems that NACT plays a more and more important role than ever on an overall treatment basis of breast cancer." (page 188, lines 2 to 8)

"Regarding side effects and complication of NACT, all the reporters cited in this article and referring to the side effects mention that the respective regimens undergo side effects that are commonly developed. It does not cause any trouble in implementing surgery, nor does it adversely affect the wound healing after surgery." (page 191, lines 18 to 20)

(D) Conclusion

"neoadjuvant chemotherapy is a new therapeutic strategy, and there is a theoretical ground suggesting the possibility of having higher therapeutic effects in comparison to adjuvant (postoperative) chemotherapy. It has not been demonstrated at present that it is superior in terms of the recurrence-free duration, overall survival, and cure rate. For the purpose of local control, however, it is definitely demonstrated to make surgery and radiation therapy easier and make breast

conservation highly possible. Therefore, as long as it is safe and it has at least an effect comparable to that of adjuvant (postoperative) chemotherapy in recurrence-free duration and overall survival, it seems to be worth proceeding a clinical study for its utility by further adding an improvement as one alternative for the treatment in all disease stages." (page 195, lines 2 to 9)

B Exhibit Ko 16 (Tadashi Kobayashi et al., "Neoadjuvant Chemotherapy for locally-advanced breast cancer" "Clinical of breast cancer", Vol. 11, No. 3, pages 441 to 454, September 1996), a publication distributed before the priority date, has the following description (the line number of cited part is the line number from which Tables and their explanation were excluded.):

(A) Introduction

"Locally advanced breast cancer (LABC) is not definitely defined. It falls within stage IIB, III, and stage IV that becomes M1 by local evolution without distant metastases of TNM category (UICC1987), and it particularly shows stage III (sometimes including locally-advanced stage IV). Inflammatory breast cancer is treated as LABC. For the improvement on the outcome from therapy of this locally-advanced breast cancer with adverse prognosis, a multidisciplinary approach including neoadjuvant therapy (NAT) (synonym: primary, induction, initial, preoperative, etc.) was begun in Milan Cancer Institute in 1973 and in the United States M.D. Anderson Hospital in 1974.

NAT means drug therapy (chemotherapy) that precedes local therapy (surgery, radiation therapy) against primary solid tumor, and is implemented as a part of a multidisciplinary approach, and it is often the case that the local therapy is followed by adjuvant chemotherapy (ACT)." (page 441, line 28 to page 442, line 6)

(B) Therapeutic strategy against locally-advanced breast cancer

"According to multicenter data as shown in the annual meeting of ASCO (American Society of Clinical Oncology) in 1990, the outcome from therapy was 5-year survival rate of 33% for 9055 cases of stage III breast cancer, and 5-year survival rate of 5% for 124 cases of inflammatory breast cancer, which were extremely poor. ...

For such adverse prognosis, a multidisciplinary approach in combination with operative therapy, radiation therapy, and drug therapy (chemotherapy, endocrine therapy) was implemented. In particular, a multidisciplinary approach including NAT is supposed to be a therapeutic strategy commonly recognized at present (Hortobagyi), and recommended in the textbook as a standard therapeutic strategy.

This therapeutic strategy exhibited the most drastic effect in a case of inflammatory breast cancer. Although local therapy only resulted in death for almost

all the cases, we are seeing more and more reports that the introduction of this treatment method results in a five-year survival rate of 35 to 60% as a common outcome. ..." (page 442, lines 11 to 24)

(C) The purpose of Neoadjuvant therapy

"NAT in multidisciplinary approach has the following two major objectives:

1) Topical control

Reducing effect of primary tumors or locally-developed focus allows for easier and more conservative local therapy to minimize functional and beauty damage after surgery. In breast cancer, the success or failure of local control by NAT is linked to the possibility of breast conservation. The possibility of breast conservation generally greatly affects QOL of females.

2) The extension of disease-free interval (DFI) and overall survival (OS) and the improvement on cure rate

For systemic micrometastases, the treatment starts in an earlier stage to reduce micrometastases, and causes curing." (page 442, line 29 to page 443, line 4)

(D) Clinical problem and recent knowledge of Neoadjuvant therapy

"As aforementioned, the conclusion of randomized trial has not yet been obtained; however, the recurrence-free duration and overall survival are likely to be improved by NAT including the result of phase II study, and it is assumed at least not to be poor, and there are documents with a similar opinion." (page 445, lines 25 to 28)

"The introduction of NAT causes down staging by its relatively high response rate, and increases the opportunity of breast conservation. It is demonstrated from reports including Bonadonna et al. and Jacquillat et al. that breast can be conserved at a high rate after NAT, and Powles et al. suggest in a randomized trial of Table 2 that NAT can conserve breast at a significantly high rate compared to ACT, which apparently shows that a local control as one goal of NAT has been achieved." (page 445, lines 31 to 35)

(E) Prospective of multidisciplinary approach involving Neoadjuvant therapy

"A new anticancer agent such as a taxane (docetaxel, paclitaxel) or vinorelbine is coming on stage against breast cancer as well as anti-angiogenic agent. A clinical test has been started in a NAT region. Phase II study, randomized study of regimen including Taxane has been started in NSABP, Milan NCI and the other facilities, and great attention is paid due to its high response rate as a single agent by its nature of a non-cross resistant drug." (page 448, lines 19 to 23)

(F) Conclusion

"For the purpose of local control, however, neoadjuvant therapy is

demonstrated to make surgery and radiation therapy easier and make the breast conservation highly possible. Therefore, a method assumed to be compared favorably with adjuvant (postoperative) therapy in relatively safe, recurrence-free duration, and overall survival may possibly become one alternative of treatment in breast cancer of all stages necessary for systemic adjuvant therapy as long as there is only a benefit to increase at least the opportunity of breast conservation. However, the recurrence-free rate and overall survival of locally-advanced breast cancer are far from a level to be satisfied by the introduction of the current neoadjuvant therapy. It is supposed that it is necessary to advance the aforesaid development of a more effective multidisciplinary approach that is embedded into new therapy." (page 450, lines 18 to 26)

C Exhibit Ko 4 (William J. Gradishar, "Docetaxel as Neoadjuvant Chemotherapy in Patients with Stage III Breast Cancer", ONCOLOGY 11 (Suppl 8): 15-18, August 1, 1997), a publication distributed prior to the priority date, has the following descriptions (the description and cited part are shown by the translation):

(A) Abstract

"Optimal management of locally-advanced breast cancer (stage III) includes a combination of primary chemotherapy and subsequent surgery (if feasible) with local radiation therapy and postoperative adjuvant chemotherapy involving or not involving hormone therapy." (page 1, lines 2 to 4)

(B) Introduction

"In an initial study, the introduction of chemotherapy significantly decreases a size of primary tumor, thereby resulting in an increased number of candidates for breast conservation by a combination of surgery and radiation. In this case, the advantage of using neoadjuvant chemotherapy is to clinically and pathologically evaluate the reaction of tumors against therapy with chemotherapeutic agents." (page 1, lines 6 to 9)

(C) Treatment plan

"Patients with stage III locally-advanced breast cancer were first treated with 100 mg/m^2 docetaxel to be administered as an intravenous infusion over 1 hour once every three week by four-cycles. After four-cycle docetaxel, the patients were subjected to breast conservation surgery or excision of the breast. Doxorubicin/cyclophosphamide chemotherapy (four cycles of 60 mg/m^2 adriamycin and 600 mg/m^2 cyclophosphamide) in standard dose was started after surgery." (page 1, lines 11 to 15)

D In addition to the aforesaid items A to C, according to the aforesaid (1)B and

C, a person ordinarily skilled in the art who had the following common technical knowledge about the therapy of operable breast cancer as of the priority date (May 14, 1999).

(A) Neoadjuavnt therapy (NAT) is a drug therapy (chemotherapy) that is implemented prior to local therapy (surgery, radiation therapy) for primary solid tumor, and is implemented as a part of a multidisciplinary approach (aforesaid item A(A), B(A), aforesaid (1)B(B)).

It is often the case that adjuvant chemotherapy (ACT) follows local therapy (aforesaid item A(A), B(A), aforesaid (1)B(B)).

(B) In breast cancer, neoadjuvant therapy was introduced as a part of a multidisciplinary approach in locally-advanced breast cancer in the first half of the 1970's (aforesaid item A(A)(C), B(A), aforesaid (1)B(B)(C), C(F)).

A primary objective of neoadjuvant therapy is to allow for local therapy in a case where a local therapy is difficult, by a reducing effect of primary tumors or locally-developed focus, whereas it allow for easier and more conservative local therapy to minimize functional and beauty damage after surgery in a case where a local therapy is feasible. In breast cancer, the success or failure of local control leads to the success or failure of breast conservation, and generally greatly affects QOL of females.

A second purpose of neoadjuvant therapy is to start treatment in an earlier stage for systemic micrometastases, eradicate micrometastases, extend disease-free interval and overall survival, and finally improve a cure rate. (aforesaid item A(B), B(C), aforesaid (1)B(B), C(F))

Neoadjuvant therapy makes surgical therapy and radiation therapy easier in the first objective of local control, and makes breast conservation possible at a high rate, and it would not be at least inferior to adjuvant chemotherapy in terms of the second objective of recurrence-free duration and overall survival (aforesaid items A(C)(D), B(B)(D)(F), aforesaid items (1)B(B)(C)(G), C(F)).

A multidisciplinary approach where neoadjuvant therapy is introduced is believed to be a commonly accepted therapeutic strategy in a locally-advanced breast cancer that could often be stage III, and is also introduced into earlier stages I, II (aforesaid items A(C)(D), B(A)(B)(F), C(A), aforesaid item (1)B(G)).

(C) With the aforesaid (A)(B) as a backdrop, it is a common therapy in operable breast cancer to conduct neoadjuvant chemotherapy, and then surgically remove tumors, and further conduct adjuvant chemotherapy (aforesaid C(A)(C), aforesaid (1)B(E)).

(3) Development of anticancer drug

A In the "Guideline of clinical evaluation of anticancer agent" attached to "Regarding 'Guideline of clinical evaluation of anticancer agent'" (New Drug No. 9) dispatched on February 4, 1991 by Chief of New Pharmaceuticals Division of the Pharmaceutical Affairs Bureau (Ko 42), the following matters are described:

(A) In a Phase I test, a consideration is mainly given to safety. Subject patients satisfy a condition that "To have malignant tumor for which a standard therapy has no effect, or lack of commonly accepted standard therapy as of participation in a clinical test. But it is unnecessary to have an objectively measurable lesion".

(B) In a Phase II test, consideration is given to antitumor effect and safety. In principle, the subject patients satisfy a condition that "for whom the conventional standard therapy is no longer ineffective, or for whose disease an appropriate therapy is not established, with the proviso that a clinical trial is implemented for cases of initial treatment in the late phase II test".

(C) In a Phase III test, clinical effects are considered with a focus on survival advantage. In principle, the targeted patients are required to satisfy a condition that "target cases where a drug therapy is used to meet the indications, and in principle target cases of an initial treatment".

B According to Exhibit Ko 36 (a webpage titled "Breast Cancer Survival Rates" of American Cancer Society, finally revised on August 18, 2016), 5-year relative survival rate of breast cancer for every stage is [i] 100% for females with stage 0 or stage I breast cancer, [ii] about 93% for females with stage II breast cancer, [iii] about 72% for females with stage III breast cancer, and [iv] about 22% for females with metastatic or stage IV breast cancer.

Further, Exhibit Ko 37 (JOYCE O'SHAUGHNESSY, "Extending Survival with Chemotherapy in Metastatic Breast Cancer", The Oncologist 2005; 10 (suppl 3): 20-29, 2005) discloses that "metastatic breast cancer (MBS) cannot yet be treated substantially, and the purpose of treatment includes the extension of overall survival to the extent that does not have a negative effect on alleviation of symptoms, delay of progression of lesion, and quality of life".

Besides, taking into account the aforesaid item (1)C(C) and Exhibit Ko 44, page 54, metastatic breast cancer corresponds to "one for which the conventional standard therapy is no longer ineffective, or an appropriate therapy is not established" as of the priority date (May 14, 1999).

C Exhibit Ko 43 ("Nanzando Medical Dictionary 18th Edition", January 16,

1998), a publication distributed before the priority date, discloses in the comment of "primary cancer" that "Tissue image of metastatic foci is fundamentally the same as that for primary tumors, but may sometimes mimic the structure of involved organ tissues or show a tissue image highly differentiated or low differentiated to primary tumors."

D In addition to the aforesaid items A to C, according to the aforesaid (1)B(F) and C(A)(F), it was recognized as a matter of common technical knowledge as of the priority date (May 14, 1999) for a person ordinarily skilled in the art that Phase I test and Phase II test of clinical test were implemented for patients with metastatic breast cancer as targeted patients to confirm anticancer effects on patients with operable breast cancer by taking into account anticancer effects in the development of therapeutic agents for breast cancer, which are included in anticancer drugs.

3 Reason 3 for rescission (Errors in the determination of the inventive step over Exhibit Ko 1 as a main cited reference)

In view of the circumstances, a consideration is given first to Reason 3 for rescission.

(1) Finding of Exhibit Ko 1 invention

According to Ko 1 of the aforesaid 2(1)A, Exhibit Ko 1 describes the following Exhibit Ko 1 invention.

"A pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-HER2 antibody for the treatment of a human patient who has been diagnosed with breast tumor where HER2 protein is overexpressed, the treatment comprising (a) treating the patient with the pharmaceutical, or the pharmaceutical and a therapeutically effective amount of a chemotherapeutic agent such as paclitaxel, anthracycline, cyclophosphamide, doxorubicin, or epirubicin."

(2) Finding of different feature between Patent Invention 1 and Exhibit Ko 1 invention

Patent Invention 1 and Exhibit Ko 1 invention have the following item A in common and differ from each other in the following Different feature 1 of the following item B:

A Common points

"A pharmaceutical comprising a therapeutically effective amount of humanized 4D5 anti-ErbB2 antibody for the treatment of a human patient who has been diagnosed with breast tumor where ErbB2 protein is expressed"

B Different feature 1

Patent invention 1 applies the pharmaceutical to the treatment that comprises

implementing the steps of (a) treating a patient with the pharmaceutical, (b) surgically removing a tumor; and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent in this order, whereas Exhibit Ko 1 invention fails to specify the application of the pharmaceutical to the treatment that comprises implementing such steps sequentially.

(3) Whether Different feature 1 was easily conceivable

A(A) A pharmaceutical of Exhibit Ko 1 invention is a pharmaceutical comprising a therapeutically effective amount of anti-HER2 antibody. According to the aforesaid 2(1)E, it was recognized as a matter of common technical knowledge as of the priority date that: [i] Anti HER2 antibody binds to extracellular area of HER2 protein to suppress the growth of breast cancer cells that overexpress HER2 protein and show antibody-dependent cellular cytotoxicity (ADCC); [ii] HER2 protein overexpression is observed in 25% to 30% of early stage breast cancers in addition to metastatic breast cancer; [iii] In a clinical test of patients with metastatic breast cancer having tumors overexpressing HER2 protein, compared to a single administration group of a specific chemotherapeutic agent including paclitaxel, a coadministration group of the chemotherapeutic agent and anti-HER2 antibody has extended time to disease progression, improved overall response rate (ORR), extended median of response duration, and improved one-year survival rate, which promotes antitumor effects; and [iv] In a clinical test of anti-HER2 antibody, there was a trend showing that cases with a stronger expression of HER2 protein were more excellent in both antitumor effect and time-to-tumor progression in both cases of single agent administration and coadministration with a chemotherapeutic agent.

Further, according to the aforesaid 2(3)D, it was recognized as a matter of common technical knowledge as of the priority date to confirm anticancer effects on patients with operable breast cancer by taking into account anticancer effects on patients with metastatic breast cancer in the development of therapeutic agents for breast cancer.

Further, Exhibit Ko 2 titled "future trend of neoadjuvant therapy for breast cancer", which is a publication distributed before the priority date, discloses that "The role of these new strategies in combination with primary chemotherapy should be evaluated by early-stage breast cancer patients" right after introducing a clinical test where anti-HER2 antibody and doxorubicin or cyclophosphamide are coadministered to metastatic breast cancer patients (aforesaid 2(1)B(A)(F)). Taking the above into account, it is recognized that a person ordinarily skilled in the art who read Exhibit Ko 1 would have easily conceived of applying a therapeutically effective amount of a

pharmaceutical of Exhibit Ko 1 invention including anti-HER2 antibody for the treatment of operable breast cancer that overexpresses HER2 protein.

(B) According to the aforesaid 2(1)E, (2)D, it was a matter of common technical knowledge as of the priority date that [i] it was demonstrated in breast cancer that the success or failure of breast conservation greatly affected QOL (quality of life) of females in general, whereas neoadjuvant therapy made surgery easier and made breast conservation possible at a high rate; [ii] in operable breast cancer, it was a common therapy for operable breast cancer to implement neoadjuvant chemotherapy, and then surgically remove tumors and further implement adjuvant chemotherapy; and [iii] In a clinical test of patients with metastatic breast cancer having tumors overexpressing HER2 protein, compared to a single administration group of a specific chemotherapeutic agent including paclitaxel, a coadministration group of the chemotherapeutic agent and anti-HER2 antibody has extended time to disease progression, improved overall response rate (ORR), extended median value of response duration, and improved one-year survival rate, in which the promotion of antitumor effects was observed. Further, with an introduction that coadministration of anti-HER2 antibody and a chemotherapeutic agent such as paclitaxel against metastatic breast cancer patients with HER2 overexpression has superior overall remission rate and a median time-to-tumor progression as compared to a single administration of a chemotherapeutic agent, Exhibit Ko 3, a publication distributed before the priority date, discloses that "Novel chemotherapeutic strategies that prove successful in the metastatic and adjuvant settings may potentially also find application in neoadjuvant treatment" (aforesaid 2(1)C(E)(F)).

Further, Exhibit Ko 2 titled "future trend of neoadjuvant therapy for breast cancer", which is a publication distributed before the priority date, discloses that "The role of these new strategies in combination with primary chemotherapy should be evaluated by early-stage breast cancer patients" right after introducing a clinical test where anti-HER2 antibody and doxorubicin or cyclophosphamide are coadministered to metastatic breast cancer patients (aforesaid 2(1)B(A)(F)). Taking the above into account, it is recognized that a person ordinarily skilled in the art who read Exhibit Ko 1 could have easily conceived of coadministering a pharmaceutical of Exhibit Ko 1 invention with a chemotherapeutic agent before surgery, conducting a surgery, and further coadministering the pharmaceutical of Exhibit Ko 1 invention with the chemotherapeutic agent after surgery for the treatment of operable breast cancer that overexpresses HER2 protein.

B(A) Defendant alleges that as of the priority date, an action mechanism of

Trastuzumab in a living body was still a subject of research, and a dosage regimen had been considered continuously for chemotherapy, there was no document to suggest administering an antibody before surgery for the treatment of breast cancer, and thus a person ordinarily skilled in the art could not have conceived of administering a novel antibody just approved in place of, or in addition to, a preoperative administration of a chemotherapeutic agent whose efficacy had already been confirmed.

As the aforesaid items A, however, a person ordinarily skilled in the art could have easily conceived of coadministering anti-HER2 antibody, a pharmaceutical of Exhibit Ko 1 invention, with a chemotherapeutic agent before surgery.

Further, as per the aforesaid 2(1)E, it is recognized that anti-HER2 antibody has cardiotoxicity, and might cause ventricular dysfunction and congestive heart failure by administration. A pharmaceutical of Exhibit Ko 1 invention is approved as a pharmaceutical formulation for metastatic breast cancer patients. It cannot be recognized that there is a safety problem that raises the indications against operable breast cancer patients.

(B) Defendant alleges that Exhibit Ko 2 definitely states in the whole disclosure that in the optimal treatment regimen, chemotherapy is first implemented, and the other therapy is implemented thereafter. However, Exhibit Ko 2 is an article titled "future trend of neoadjuvant therapy for breast cancer" and discloses that "The role of these new strategies in combination with primary chemotherapy should be evaluated by early-stage breast cancer patients" right after introducing a clinical test where anti-HER2 antibody and doxorubicin or cyclophosphamide are coadministered to metastatic breast cancer patients. Thus it is suggested that anti-HER2 antibody and chemotherapy are prescribed in combination before surgery for patients with early-stage breast cancer. As in the aforesaid item A, it can be said that the description of Exhibit Ko 2 motivates us to coadminister anti-HER2 antibody of the pharmaceutical of Exhibit Ko 1 invention with a chemotherapeutic agent before surgery.

(C) Defendant alleges that cells of cancer with a high metastatic risk (cancer that has been already metastasized) have different properties from cancer cells that remain at a primary site.

As aforesaid item 2(3)C, however, it was believed as of the priority date that a tissue image of metastatic foci was fundamentally the same as that of primary tumors in cancers. Defendant fails to allege specifically the reason why the difference in properties between cells of metastatic breast cancer that overexpress HER2 protein

and cells of operable breast cancer that overexpress HER2 protein can be a barrier to apply anti-HER2 antibody (targeted drug) binding to an extracellular region of HER2 protein to cells of operable breast cancer that overexpress HER2 protein. There is no evidence to show the fact that the difference in properties between cells of metastatic breast cancer that overexpress HER2 protein and cells of operable breast cancer that overexpress HER2 protein can be a barrier to apply anti-HER2 antibody (targeted drug) binding to an extracellular region of HER2 protein to cells of operable breast cancer that overexpress HER2 protein.

Therefore, it cannot be recognized that the above Defendant's argument affects the determination of the aforesaid item A.

(4) Effects of Patent invention 1

A As in the aforesaid item 1, the corrected description does not show any result of clinical test as the effects of Patent invention 1. "Patients treated according to the above therapeutic regimen will display improved overall survival and/or reduced time to tumor progression (TTP)." ([0119])

Incidentally, it can be seen from the description of each publication of the aforesaid item 2(1)(2) that the overall survival and time-to-tumor progression (TTP) are common barometers to measure the effect of an anticancer drug in breast cancer. The above description of the corrected description fails to describe a standard for comparison and a degree of the effectiveness (e.g. whether to be a case where only surgery is implemented, or a case where surgery and postoperative chemotherapy are implemented, or a case where preoperative chemotherapy, surgery, and postoperative chemotherapy are implemented, or a case where preoperative chemotherapy and surgery and postoperative administration of anti-HER2 antibody are implemented, or a case where the administration of anti-HER2 antibody was only implemented for operable breast cancer) with respect to the improved survival rate and the extended time-to-tumor progression (TTP) achieved. Further, a standard for comparison and the effectiveness cannot be inferred from the description of the corrected description by a person ordinarily skilled in the art.

Consequently, it is reasonable to think that Patent invention 1 only has qualitative effects of improved overall survival and extended time-to-tumor progression (TTP) compared to the cases where a pharmaceutical of Patent invention 1 is not administered.

Further, as the aforesaid item 2(1)A, Exhibit Ko 1 discloses that, when a pharmaceutical of Exhibit Ko 1 invention is coadministered with a specific chemotherapeutic agent of ([i] paclitaxel, [ii] anthracycline [doxorubicin or

epirubicin], and cyclophosphamide) to metastatic breast cancer patients with tumors that overexpress HER2 protein, a time-to-tumor progression is significantly prolonged and survival rate for one year is improved compared to patients in which the chemotherapeutic agent is solely administered. Therefore, a person ordinarily skilled in the art could expect that the pharmaceutical of Exhibit Ko 1 invention had qualitative effects of improved overall survival and extended time-to-tumor progression (TTP) for patients with metastatic breast cancer that overexpresses HER2 protein. A person ordinarily skilled in the art could expect that, when a pharmaceutical of Exhibit Ko 1 invention is applied to an operable breast cancer that overexpresses HER2 protein by a process of Patent invention 1, it has qualitative effects of improved overall survival and extended time-to-tumor progression (TTP) compared to the cases where a pharmaceutical of Exhibit Ko 1 invention is not administered.

B Defendant alleges that it is reasonable to refer to specific experimental data on the basis of the qualitative description of the effect of the invention of the corrected description, and thus Patent invention 1 has a significant effect on the basis of Exhibits Ko 17, 19 [Trial Exhibits Otsu 1, 3].

As in the aforesaid item A, however, it can be learned or inferred from the description of the corrected description that Patent invention 1 only has qualitative effects of improved overall survival and extended time-to-tumor progression (TTP) compared to the cases where a pharmaceutical of Patent invention 1 is not administered. Therefore, even if a consideration is given to the experimental data of Exhibits Ko 17, 19 [Trial Exhibits Otsu 1,3], publications after the priority date, to the extent that shows the above qualitative effects within the description of the corrected description, as in the aforesaid item A, the above qualitative effects can be expected by a person ordinarily skilled in the art. Thus it cannot be said to be a significant effect. On the other hand, it goes beyond the scope of the description of the corrected description to consider the experimental data of Exhibits Ko 17, 19 [Trial Exhibits Otsu 1, 3] beyond the above qualitative effects. Thus this cannot be seen as the effects of Patent invention 1. This holds true for Exhibits Ko 18, 20, 21 [Trial Exhibits Otsu 2, 4, 5], which are the remaining publications after the priority date.

Therefore, as for Exhibits Ko 17 to 21 [Trial Exhibits Otsu 1 to 5], which are publications published after the priority date, without considering the specific contents, it cannot be said that Patent invention 1 has a significant effect.

(5) Summary of Patent invention 1

As aforementioned, it can be recognized that Patent invention 1 was easily

conceivable by a person ordinarily skilled in the art on the basis of Exhibit Ko 1 invention and the matters described in Exhibits Ko 1 to Ko 4.

(6) Patent inventions 2 to 8

As per the aforesaid item (3)A, it is recognized that a person ordinarily skilled in the art who read Exhibit Ko 1 could have easily conceived of coadministering a pharmaceutical of Exhibit Ko 1 invention with a chemotherapeutic agent before surgery, and conducting a surgery, and further coadministering the pharmaceutical of Exhibit Ko 1 invention with the chemotherapeutic agent after surgery for the treatment of operable breast cancer that overexpresses HER2 protein.

Further, as aforesaid item (1), Exhibit Ko 1 invention includes the step of treating patients with a pharmaceutical of Exhibit Ko 1 invention and a therapeutically effective amount of paclitaxel. If the pharmaceutical of Exhibit Ko 1 invention (anti-HER2 antibody) is combined with paclitaxel, the high combined effect is described in Exhibit Ko 1 (aforesaid item 2(1)A(F)). Therefore, a person ordinarily skilled in the art could have easily conceived of using paclitaxel as the chemotherapeutic agent to be coadministered before surgery or using paclitaxel as the chemotherapeutic agent to be coadministered after surgery.

Further, the effects of Patent inventions 2 to 8 are expectable by a person ordinarily skilled in the art, similar to the aforesaid item (4).

Consequently, Patent inventions 2 to 8 were easily conceivable by a person ordinarily skilled in the art on the basis of Exhibit Ko 1 invention and the matters described in Exhibits Ko 1 to 4.

(7) Patent invention 9

Patent invention 9 is an article of manufacture comprising a container, a pharmaceutical of Patent invention 1 contained in the container, and a package insert instructing users of the composition "to treat a patient in principle by implementing the following steps in the following order of: (a) treating the patient with the pharmaceutical; (b) surgically removing a tumor; and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent".

As per the aforesaid item 2(1)A(I), HERCEPTIN is supplied in a "vacuum vial". It was a matter of common technical knowledge as of the priority date to include a container for a pharmaceutical as a constituent element in an article of manufacture for supplying a pharmaceutical.

Further, as is obvious from a package insert of Herceptin, Exhibit Ko 1, it was a matter of common technical knowledge as of the priority date to include a package insert (the corrected description, [0052]) describing a regimen as a constituent

element in an article of manufacture for supplying a pharmaceutical. Further, a package insert of Patent invention 9 describes a regimen of a pharmaceutical of Patent invention 1.

As aforementioned, it can be recognized that Patent invention 9 was easily conceivable by a person ordinarily skilled in the art on the basis of Exhibit Ko 1 invention and the matters described in Exhibits Ko 1 to Ko 4.

4 Conclusion

In view of the foregoing, Reason 3 for rescission has a point, and thus a trial decision was made illegally so as to affect the conclusion without considering the remaining reasons for rescission. Therefore, the court shall accept the Plaintiff's claim, and renders as in the main text.

Intellectual Property High Court, Second Division

Presiding Judge MORI Yoshiyuki
Judge MORIOKA Ayako
Judge FURUSHO Ken

(Attachment)
List of Parties concerned

Plaintiff Celltrion incorporated

(omitted)

Plaintiff's supporting intervener Pfizer Inc.

(omitted)

Defendant Genentech, Incorporated

(omitted)